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Original Communications

THE VOLUME OF THE UTERUS DURING LABOR AND ITS CORRELATION WITH BIRTH WEIGHT

I. A Method for the Prediction of Birth Weight

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OBSTETRICIANS have always sought accurate ways to determine the size, weight, and maturity of the fetus. There is still no reliable method which successfully overcomes the obstacles and variables provided by nature.

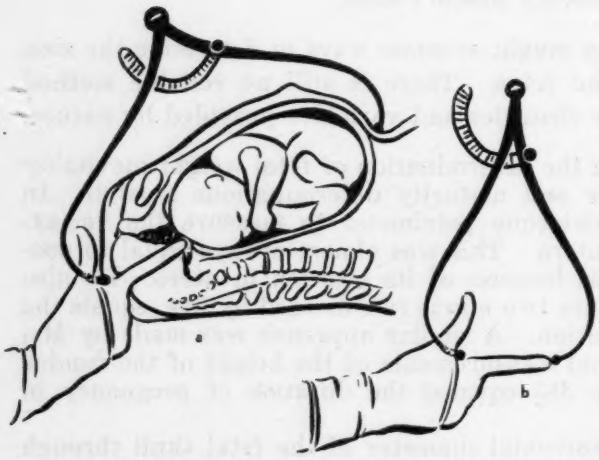
A review of the literature on the determination of fetal weight inevitably involves the survey of fetal size and maturity determinations as well. In 1871, Ahlfeld[1] utilized the Baudelocque pelvimeter to measure the vertex-coccyx distance of the fetus in utero. This was almost always equal to one-half the total length of the fetus because of its position in utero. He also found that this same distance, times two minus two divided by five, equals the number of lunar months of gestation. A similar approach was made by McDonald[2] in 1906 who used external measurements of the height of the fundus in centimeters. This divided by 3½ equaled the duration of pregnancy in lunar months.

Perret[3] measured the occipitofrontal diameter of the fetal skull through the abdominal wall of the mother. He found that the biparietal diameter is about 2.5 cm. less than the occipitofrontal diameter and that the biparietal is directly related to length of gestation. In 1911, Zangemeister[4] weighed and measured fetuses of various ages. He then graphed the measurements against length of gestation using the first day of the last menstrual period as the zero point of the graph. He plotted one line for the average of all the cases and one each for maximum and minimum values. In 1942, Andreas[5] tried to determine fetal length and maturity by taking x-rays at standard distances and in standard positions. In 1948, Donaldson and Cheney[6] utilized the x-ray to calculate the fetal cephalic volume. Although the cephalic dimensions and the weight of the fetus varied widely, they felt it was still the best available

method of weight prediction to date. There does not seem to be any relation between the maternal weight gain and the weight of the fetus,[7] nor can the length of gestation be correlated with weight or length of the fetus.[8] Although many other papers have been written on this and related subjects,[9-16] there does not seem to be any reliable method to determine fetal weight.

A. Measurement of the transverse diameter.

B. Measurement of the external longitudinal diameter.



C. a. Measurement of the rectal longitudinal diameter

b. Subtraction of the length of finger

D. Measurement of the abdominal wall thickness

Fig. 1.

Method

1. Basic Theory.—

A fundamental physical law states that for a given homogeneous mass the weight of the mass is directly proportional to its volume, where the density is constant (W = DV). In applying this physical fact to the birth weight of the infant and the volume of the uterus, it is obvious that the volume of the uterus is not accurately known, and certain assumptions must be made.

Moreover, the uterus, placenta, fetus, amniotic fluid, etc., do not form a homogeneous mass, but if the assumed volume of the uterus correlates well with the actual birth weight, the nonhomogeneity of the mass may be ignored.

2. Theoretical Volume of the Uterus.—

The volume of the uterus was assumed to be either a sphere, or an ellipsoid (an ellipse rotated around its long axis). The volume of a sphere is given by the equation, $V = \pi/6\ D^3$, where D is the diameter of the sphere. The volume of an ellipsoid is given by the equation, $V = \pi/6\ LT^2$, where L is the longitudinal and T the transverse diameter.

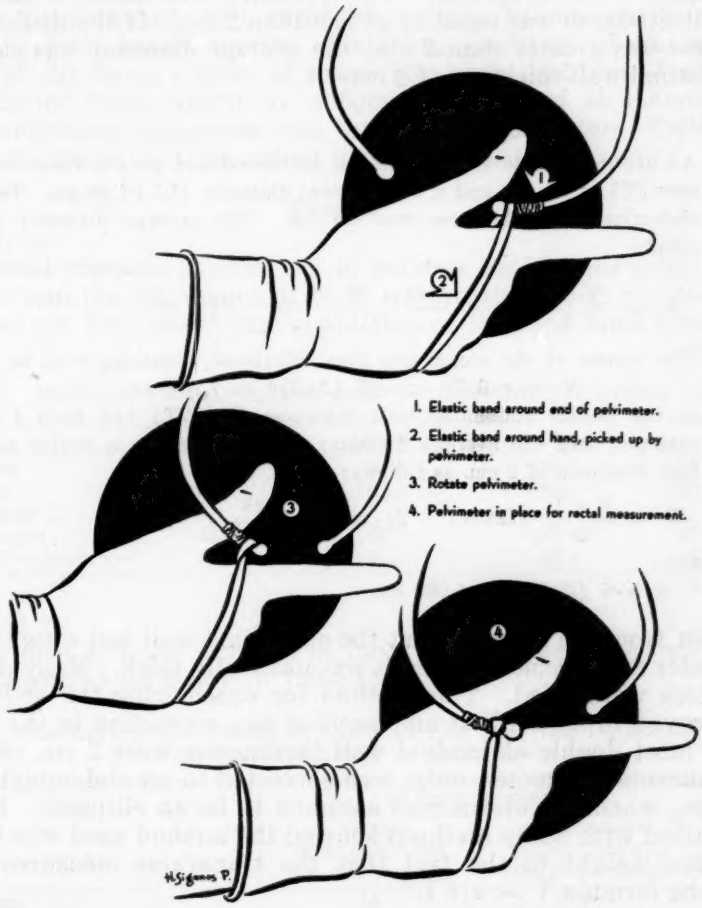

1. Elastic band around end of pelvimeter.
2. Elastic band around hand, picked up by pelvimeter.
3. Rotate pelvimeter.
4. Pelvimeter in place for rectal measurement.

Fig. 2.—Method for securing pelvimeter to hand for rectal measurements.

3. Measurements Made for the Calculation of the Theoretical Volume of the Uterus.—

The transverse and longitudinal diameters of the uterus, and the abdominal wall thickness were measured (Fig. 1).

A. The transverse diameter was taken as the widest transverse diameter of the uterus (Fig. 1, *A*). This was usually found to be above the level of the umbilicus.

B. The longitudinal diameter of the uterus was measured either externally, or rectally. The external longitudinal diameter was taken from

the superior border of the symphysis to the top of the fundus (Fig. 1, *B*). The rectal longitudinal diameter was taken as shown in the illustration (Fig. 1, *C*). Of particular importance was the manner in which the pelvimeter was secured to the examining hand (Fig. 2). The transverse and longitudinal diameters were measured with the uterus relaxed, and contracted.

C. The abdominal wall thickness was measured by grasping the abdominal wall below the level of the umbilicus, folding it, and measuring the double wall thickness (Fig. 1, *D*).

4. Calculation of the Theoretical Volume of the Uterus.—

Assuming the uterus to be a sphere, the average of the transverse and longitudinal diameters was calculated. No correction was made, if the double abdominal wall thickness was equal to or less than 2 cm. If the double abdominal wall thickness was greater than 2 cm., the average diameter was corrected to a double abdominal wall thickness of 2 cm.

Examples:

1. An external measurement with the uterus relaxed gave a transverse diameter (T) of 21 cm. and a longitudinal diameter (L) of 28 cm. The double abdominal wall thickness was 1.5 cm. The average diameter (D) was simply

$$D = \frac{T + L}{2} = \frac{21 + 28}{2} = 24.5 \text{ cm.}$$

The volume of the uterus was then calculated, assuming it to be a sphere

$$V = \pi/6\ D^3 = \pi/6\ (24.5)^3 = 7{,}700 \text{ c.c.}$$

2. If the double abdominal wall thickness (DAWT) had been 4 cm., for example, then the average diameter was corrected to a double abdominal wall thickness of 2 cm. as follows:

$$D = \frac{T + L}{2} - (DAWT - 2) = \frac{21 + 28}{2} - (4 - 2) = 22.5 \text{ cm.}$$

and

$$V = \pi/6\ (22.5)^3 = 6{,}060 \text{ c.c.}$$

It is seen from the example that the abdominal wall had a significant effect on the diameter measurements when it was unusually thick. Many different correction factors were tried. This method for considering the abdominal wall thickness proved to be the best and avoided any correction in the majority of cases, since most double abdominal wall thicknesses were 2 cm. or less.

The transverse diameter, only, was corrected to an abdominal wall thickness of 2 cm., when the uterus was assumed to be an ellipsoid. Here, again, experimentation with many methods showed the method used was the simplest and gave due weight to the fact that the transverse measurement (T) is squared in the formula $V = \pi/6\ LT^2$.

Examples:

3. Using the values of Example 1, the volume of the uterus when assumed to be an ellipsoid was calculated as follows:
$V = \pi/6\ LT^2 = \pi/6\ (28)\ (21)^2 = 6{,}440$ c.c.
4. If the double abdominal wall thickness (DAWT) had been 4 cm., then
$V = \pi/6\ L\ [T - (DAWT - 2)]^2$
$= \pi/6\ L\ [21 - (4 - 2)]^2 = \pi/6\ (28)\ (19)^2 = 5{,}290$ c.c.

Eight different volumes were calculated for each patient. A volume was determined on the basis of (1) an external measurement with the uterus relaxed, (2) an external measurement with the uterus contracted, (3) a rectal

measurement with the uterus relaxed, (4) a rectal measurement with the uterus contracted. The uterus was first assumed to be a sphere, and then an ellipsoid.

5. Procedure.—

Forty-five pavilion patients on the delivery floor of the New York Lying-In Hospital were used in this study. None of these patients happened to have any apparent associated pathological condition such as tumors, hydramnios, or medical disease. Unusual presentations or positions were not considered in this study. All measurements were taken with the patient in a lithotomy position. The following was recorded in each case: name, history number, age, weight when nonpregnant, last recorded weight, height, parity, gravidity, position of the fetal heart, cervical dilatation, condition of the membranes, presentation of the fetus, station of presenting part, duration of uterine contraction, predicted birth weight by abdominal palpation as recorded by the admitting obstetrician, transverse and longitudinal diameters, the double abdominal wall thickness, and the actual birth weight of the infant.

Results

1. Sample.—

The physical characteristics of the 45 patients used in this study are shown in Table I. From the standpoint of birth weight, this group represents a reliable sample of the 1951 obstetrical population of the New York Lying-In Hospital.*

TABLE I. PHYSICAL CHARACTERISTICS OF 45 PATIENTS STUDIED DURING LABOR

	NO.	MEAN	S.D.	RANGE
Age (years)	45	24.3	±4.7	18 to 40
Height (cm.)	45	161.1	±5.1	151.1 to 169.9
Weight (kg.)				
Nonpregnant	45	62.7	±12.4	45.4 to 95.0
Gain in Pregnancy	45	11.1	±6.1	-9.1 to 22.7

2. Mothers.—

The gravidity and the progress of labor at the time the diameters of the uterus were measured are shown in Table II.

TABLE II. GRAVIDITY AND PROGRESS OF LABOR AT THE TIME THE DIAMETERS OF THE UTERUS WERE MEASURED IN 45 PATIENTS

	STATION OF VERTEX		
	ABOVE ISCHIAL SPINES NO. OF PATIENTS	AT OR BELOW ISCHIAL SPINES NO. OF PATIENTS	TOTAL NUMBER OF PATIENTS
A. Primigravidas	13	13	26
Multigravidas	9	10	19
B. Vertex presentation	21	24	45
C. Membranes:			
Intact (18 primigravidas)	17	18	35
Ruptured (8 primigravidas)	5	5	10

The group is divided according to the station of the vertex. In all cases, the presenting part was the vertex. In about one-half of all cases the head was not engaged. In one-half of those patients whose membranes were intact,

*During 1951 there were 4,295 total births at the New York Lying-In Hospital. Of these, 3,967 infants weighed between 2,500 and 4,999 grams. Since the actual birth weights of the sample ranged between 2,610 and 4,670 grams, the sample was evaluated on the basis of the 3,967 infants having a similar range in weights. The χ^2 of the sample is 5.48 and the 5 per cent critical value of χ^2 is 9.488.

the head was not engaged. Similarly, there was no engagement in one-half of those patients whose membranes were ruptured. The table shows clearly that the total number of patients was closely divided into two equal groups. One group had the head engaged while in the other the head was not engaged.

3. Observed or Measured Data.—

The observed or measured data are summarized in Table III. The mean of the transverse diameter is the same whether the uterus be relaxed or contracted. The mean of the longitudinal diameter is greatest when measured rectally with the uterus contracted. The range of predicted birth weights by

TABLE III. THE MEAN, STANDARD DEVIATION, AND RANGE OF OBSERVED OR MEASURED DATA OBTAINED IN 45 PATIENTS

	NO.	MEAN	S.D.	RANGE
1. External Measurement				
a. Relaxed uterus (ER)				
Longitudinal diameter (cm.)	45	28.8	±1.9	25.0 to 34.0
Transverse diameter (cm.)	45	21.2	±2.0	17.0 to 26.0
b. Contracted uterus (EC)				
Longitudinal diameter (cm.)	45	29.4	±2.1	25.5 to 36.0
Transverse diameter (cm.)	45	21.2	±1.9	17.0 to 25.0
2. Rectal Measurement				
a. Relaxed uterus (RR)				
Longitudinal diameter (cm.)	45	29.3	±2.3	24.0 to 35.0
b. Contracted uterus (RC)				
Longitudinal diameter (cm.)	45	30.5	±2.6	26.0 to 37.0
3. Double Abdominal Wall Thickness (cm.)	45	2.0	±1.09	0.5 to 7.0
4. Predicted Birth Weight by Abdominal Palpation in Grams	45	3,430	±293	2,800 to 4,200
5. Birth Weight in Grams	45	3,570	±461	2,610 to 4,670

TABLE IV. CORRELATION OF ACTUAL BIRTH WEIGHT WITH THE VOLUME OF THE UTERUS AND WITH THE ESTIMATED BIRTH WEIGHT BY PALPATION IN 45 PATIENTS (ASSUMING LINEAR REGRESSION)

		CORRELATION COEFFICIENT (r)		
		ASSUMING UTERUS TO BE		ESTIMATED BIRTH WEIGHT BY PALPATION
	NO.	SPHERE	ELLIPSOID	
A. All Cases	45			0.520 ± 0.110
1. External measurement				
Relaxed uterus	45	0.616 ± 0.094	0.561 ± 0.103	
Contracted uterus	45	0.700 ± 0.077	0.693 ± 0.078	
2. Rectal measurement				
Relaxed uterus	45	0.601 ± 0.096	0.584 ± 0.099	
Contracted uterus	45	0.750 ± 0.056	0.713 ± 0.074	
B. Station of Vertex				
1. Above ischial spines	21			0.448 ± 0.179
a. External measurement				
Relaxed uterus	21	0.836 ± 0.067	0.680 ± 0.120	
Contracted uterus	21	0.776 ± 0.089	0.742 ± 0.100	
b. Rectal measurement				
Relaxed uterus	21	0.799 ± 0.081	0.765 ± 0.093	
Contracted uterus	21	0.883 ± 0.049	0.811 ± 0.077	
2. At or below ischial spines	24			0.624 ± 0.127
a. External measurement				
Relaxed uterus	24	0.450 ± 0.166	0.401 ± 0.174	
Contracted uterus	24	0.597 ± 0.133	0.538 ± 0.148	
b. Rectal measurement				
Relaxed uterus	24	0.459 ± 0.164	0.421 ± 0.171	
Contracted uterus	24	0.608 ± 0.131	0.607 ± 0.131	

abdominal palpation (2,800 to 4,200 grams) is smaller than the range of actual birth weights (2,610 to 4,670 grams). When the birth weight was predicted by abdominal palpation, therefore, there was a tendency to underestimate large babies and to overestimate small babies. The double abdominal wall thickness ranged from 0.5 to 7.0 cm.

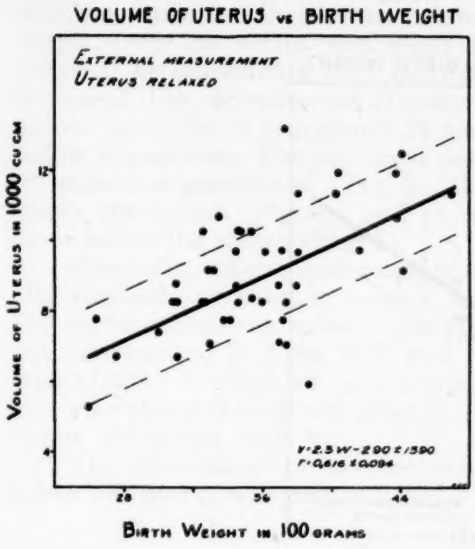

VOLUME OF UTERUS vs BIRTH WEIGHT
EXTERNAL MEASUREMENT
UTERUS RELAXED
VOLUME OF UTERUS IN 1000 CU CM
BIRTH WEIGHT IN 100 GRAMS

Fig. 3.

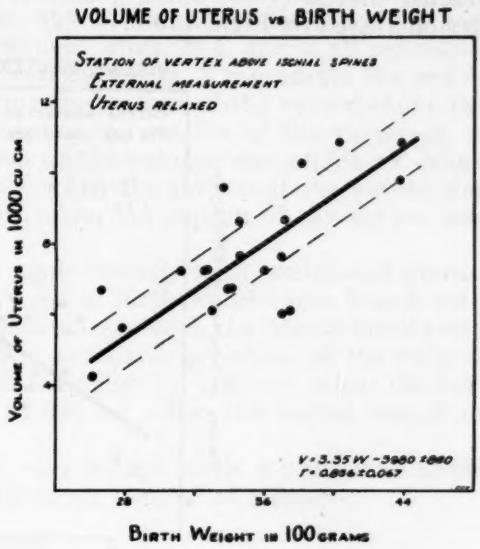

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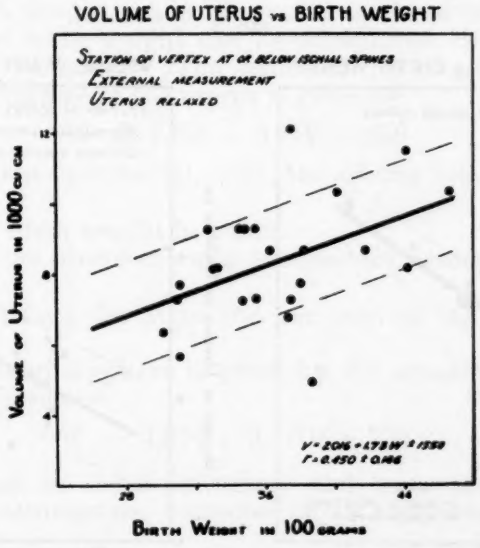
Fig. 4.


VOLUME OF UTERUS vs BIRTH WEIGHT
STATION OF VERTEX AT OR BELOW ISCHIAL SPINES
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UTERUS RELAXED
VOLUME OF UTERUS IN 1000 CU CM
BIRTH WEIGHT IN 100 GRAMS

Fig. 5.

Figs. 3, 4, and 5.—The variation in uterine volume for a given birth weight, assuming the uterus to be a sphere. External measurement with relaxed uterus. The volume varies least when the vertex is above the spines (Fig. 4).

4. Correlation.—

The correlation of actual birth weight with the volume of the uterus and with the predicted birth weight by abdominal palpation is shown in Table IV. In general, when all cases are considered, the correlation of actual birth weight with the volume of the uterus is higher than the correlation of actual birth

weight with the predicted birth weight by abdominal palpation. The correlation of actual birth weight with volume is highest when the station of the vertex is above the spines. The best correlations are found when the uterus is assumed to be a sphere, the vertex above the spines, and the measurement either external with relaxed uterus ($r = 0.836 \pm 0.067$) or rectal with contracted uterus ($r = 0.883 \pm 0.049$). These important correlations are best demonstrated by Figs. 3 to 8.

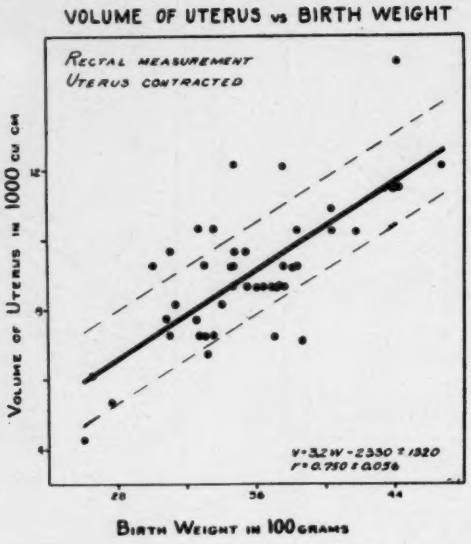
VOLUME OF UTERUS vs BIRTH WEIGHT
RECTAL MEASUREMENT
UTERUS CONTRACTED
VOLUME OF UTERUS IN 1000 CU CM
BIRTH WEIGHT IN 100 GRAMS

Fig. 6.

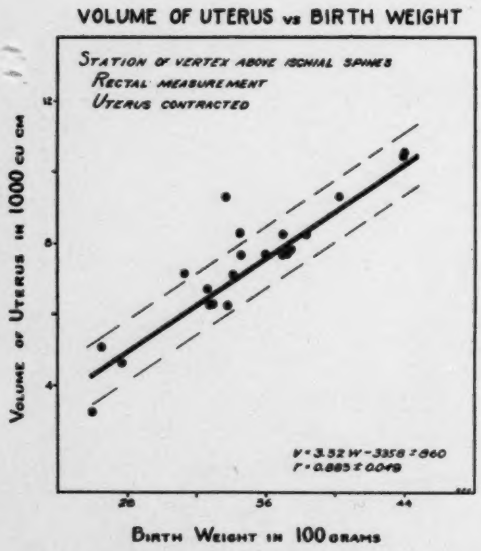
VOLUME OF UTERUS vs BIRTH WEIGHT
STATION OF VERTEX ABOVE ISCHIAL SPINES
RECTAL MEASUREMENT
UTERUS CONTRACTED
VOLUME OF UTERUS IN 1000 CU CM
BIRTH WEIGHT IN 100 GRAMS

Fig. 7.

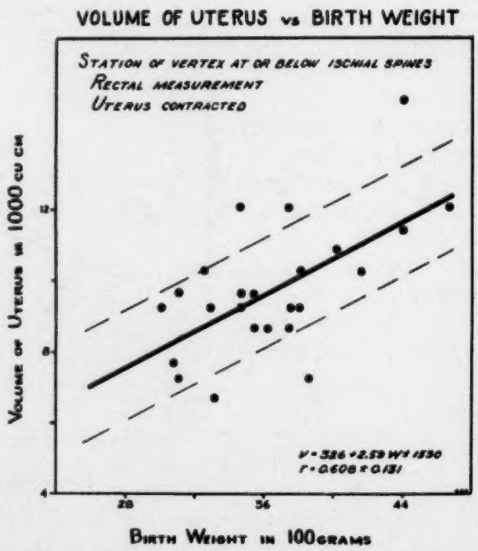
VOLUME OF UTERUS vs BIRTH WEIGHT
STATION OF VERTEX AT OR BELOW ISCHIAL SPINES
RECTAL MEASUREMENT
UTERUS CONTRACTED
VOLUME OF UTERUS IN 1000 CU CM
BIRTH WEIGHT IN 100 GRAMS

Fig. 8.

Figs. 6, 7, and 8.—The variation in uterine volume for a given birth weight, assuming the uterus to be a sphere. Rectal measurement with contracted uterus. The volume varies least when the vertex is above the spines (Fig. 7).

All of these figures are similar. The calculated volume of the uterus, assuming it to be a sphere, is plotted against the actual birth weight. The heavy line of each figure is statistically determined, and represented by the formula in the lower right-hand corner. The formula for the heavy line in Fig. 3, for example, is $V = 2.3W\text{-}290$, where V is the calculated

volume of the sphere in cubic centimeters and W is the actual birth weight in grams. The ±1,390 is the standard deviation of the volume and is represented by the two light lines. This means that at least 68 per cent of the black dots of Fig. 3 fall between ±1,390 c.c. of the heavy line. The r in the lower right-hand corner is the correlation coefficient of calculated volume with actual birth weight.

When an external measurement was made with the uterus relaxed, the smallest variation in uterine volume for any given actual birth weight was found when the vertex was above the spines. Figs. 3, 4, and 5 all represent external measurements with the uterus relaxed. Fig. 3 represents the entire 45 cases. Fig. 4 represents 21 cases having the station of the vertex above the spines, and Fig. 5 represents 24 cases having the station of the vertex at or below the spines. The standard deviation of the volume was ±1,390 c.c. when all cases are considered (Fig. 3), ±860 c.c. when the station of the vertex was above the spines (Fig. 4), and ±1,550 c.c. when the station of the vertex was at or below the spines (Fig. 5).

Similarly, when measurements were made rectally with contracted uterus, the smallest variation in volume for any given birth weight was found with the vertex above the spines. Rectal measurements with the uterus contracted are represented in Figs. 6, 7, and 8. The standard deviation of the volume was ±1,320 c.c. when all cases are considered (Fig. 6), ±860 c.c. when the vertex was above the spines (Fig. 7), and ±1,530 c.c. when the vertex was at or below the spines (Fig. 8).

The correlation of uterine volume with actual birth weight was lower when the uterus was assumed to be an ellipsoid, instead of a sphere.

Comment

The significant finding is a high correlation of the volume of the uterus with the actual birth weight, when the vertex is above the spines. Formulas for the prediction of birth weight can be established, therefore, by utilizing standard statistical methods.[17] The equation for the prediction of birth weight based on the volume of the uterus is given by

$$W = 1{,}870 + 0.21V \pm 250$$

when the measurement is external, with the uterus relaxed and the vertex above the spines.

W = predicted birth weight in grams

V = volume of the uterus in cubic centimeters, assuming the uterus to be a sphere

±250 = the standard deviation (68 per cent of the predictions will be within ±250 grams)

Since the volume of a sphere is given by the equation, $V = \pi/6\ D^3$, the prediction equation becomes

$$W = 1{,}870 + 0.11D^3 \pm 250$$

where

D = the average of the longitudinal and transverse diameters of the uterus in centimeters, corrected to an abdominal wall thickness of 2 cm.

The variation in actual birth weight for a calculated volume of the uterus, as obtained in this study, is shown in Fig. 9. At least 68 per cent of the actual birth weights fall within ±250 grams of the birth weight obtained from the heavy line of this graph.

The equation is similarly derived for a rectal measurement, uterus contracted, and vertex above the spines.

$$W = 1{,}570 + 0.23V \pm 230$$

or

$$W = 1{,}570 + 0.12D^3 \pm 230$$

Since the standard deviation is ±230 grams, the prediction of birth weight based on this measurement is slightly better than the prediction of birth weight based on external measurements with relaxed uterus, where the standard deviation is ±250 grams. The actual birth weight deviation from expected value for a determined volume of the uterus, as obtained in this study, is shown in Fig. 10.

Using the above two formulas of weight as a function of the corrected average diameter, a graph (Fig. 11) may be plotted and used for the prediction of birth weight. This is simply done by assuming values of D and calculating W. A plot of W against D is then made. The curve labeled ER is used for external measurements with uterus relaxed and vertex above the spines. For rectal measurements with contracted uterus and vertex above the spines, the curve labeled RC is used. A few examples can best demonstrate the use of the graph.

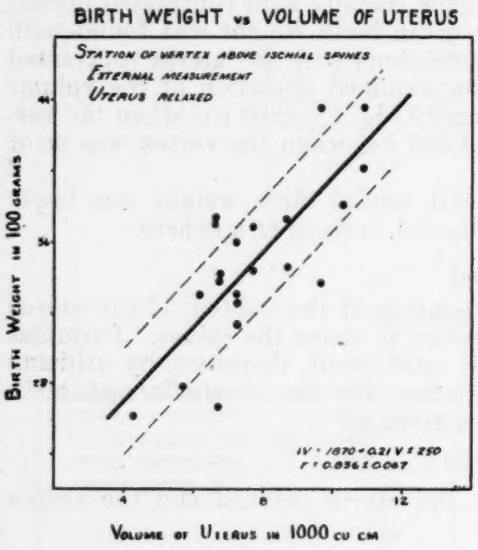
BIRTH WEIGHT vs VOLUME OF UTERUS
STATION OF VERTEX ABOVE ISCHIAL SPINES
EXTERNAL MEASUREMENT
UTERUS RELAXED
BIRTH WEIGHT IN 100 GRAMS
VOLUME OF UTERUS IN 1000 CU CM

Fig. 9.

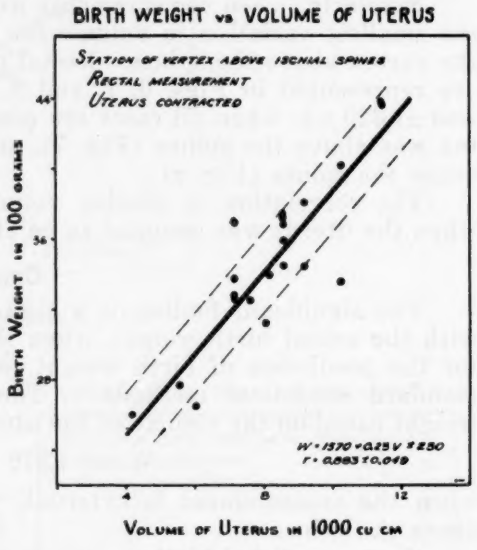
BIRTH WEIGHT vs VOLUME OF UTERUS
STATION OF VERTEX ABOVE ISCHIAL SPINES
RECTAL MEASUREMENT
UTERUS CONTRACTED
BIRTH WEIGHT IN 100 GRAMS
VOLUME OF UTERUS IN 1000 CU CM

Fig. 10.

Figs. 9 and 10.—The variation in birth weight for a calculated uterine volume, assuming the uterus to be a sphere.

Examples:

All measurements are made with the station of the vertex above the ischial spines.

5. An external measurement with uterus relaxed (ER curve) gives a transverse diameter (T) of 20 cm. and a longitudinal diameter (L) of 27 cm. The double abdominal wall thickness is 1.5 cm. The average diameter is simply

$$D = \frac{T + L}{2} = \frac{20 + 27}{2} = 23.5 \text{ cm.}$$

There is no correction for the average diameter if the double abdominal wall thickness is 2 cm. or less. The graph is then entered at an average diameter of 23.5 cm. Using the ER curve, the predicted birth weight is 3,300 grams. This means that in at least 68 per cent of the cases the weight will be 3,300 ± 250 grams. In at least 95 per cent of the cases the weight will be 3,300 ± 500 grams.

6. A rectal measurement with the uterus contracted (RC curve) gives a transverse diameter (T) of 25 cm. and a longitudinal diameter (L) of 35 cm. The double abdominal wall thickness (DAWT) is 3 cm. The corrected average diameter is

$$D = \frac{T + L}{2} - (DAWT - 2) = \frac{25 + 35}{2} - (3 - 2) = 29 \text{ cm.}$$

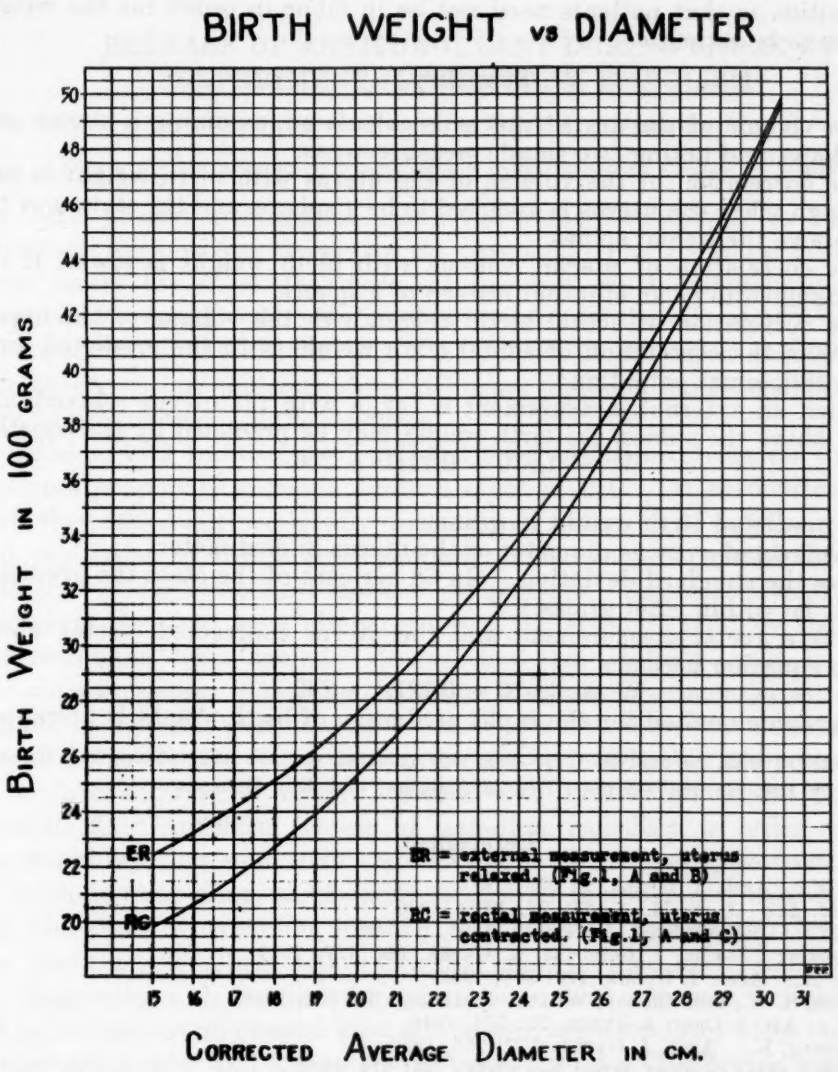

Fig. 11.—Graph for the prediction of birth weight, assuming the uterus to be a sphere.

At a corrected average diameter of 29 cm., using the RC curve, the predicted weight is 4,500 grams. The weight will be 4,500 ± 230 grams in 68 per cent of the cases and 4,500 ± 460 grams in 95 per cent of the cases.

7. The transverse diameter is 19 cm. and the longitudinal diameter is 26 cm., when a relaxed uterus is measured externally. The double abdominal wall thickness is 6 cm. Therefore,

$$D = \frac{19 + 26}{2} - (6 - 2) = 18.5 \text{ cm.}$$

The predicted birth weight is 2,570 grams, using the ER curve and entering at a diameter of 18.5 cm. The weight will be 2,570 ± 250 grams in 68 per cent of the cases.

The best estimate of birth weight is obtainable early in labor by rectal measurement with the uterus contracted, as shown by the correlation coefficient (r). Since external measurements are taken with the uterus relaxed, the supposition is that patients need not be in labor in order for the weight of the fetus to be estimated.

Summary

1. The volume of the gravid uterus is calculated, assuming a known geometrical shape, and taking two simple measurements.

2. The correlation of the volume of the uterus with birth weight is particularly high when the uterus is assumed to be a sphere, and the station of the vertex is above the ischial spines.

3. The correlation of uterine volume with birth weight is lower, if the uterus is assumed to be an ellipsoid instead of a sphere.

4. The correlation of actual birth weight with the volume of the uterus is higher than the correlation of actual birth weight with the predicted birth weight by abdominal palpation.

5. When an external measurement is taken with the uterus relaxed, and the vertex above the spines, the birth weight may be predicted by the equation

$$W = 1{,}870 + 0.11D^3 \pm 250$$

where

W = predicted birth weight in grams

D = corrected average diameter of the uterus in centimeters

±250 = the standard deviation. (In 68 per cent of the cases the predicted weight will be within ±250 grams.)

6. With a rectal measurement and the uterus contracted, vertex above spines, the equation becomes

$$W = 1{,}570 + 0.12D^3 \pm 230$$

7. A graphic method for the rapid prediction of birth weight is presented.

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RELEASE OF ANTICOAGULANT DURING SHOCK OF EXPERIMENTAL MECONIUM EMBOLISM*

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IN THE present investigation, shock was induced in animals by experimental meconium embolism; thereupon the coagulability of the blood decreased; the more severe the shock the more extreme was the incoagulability. The incoagulability was found to be largely the result of the release of a heparin-like anticoagulant to the circulation. Such release of an anticoagulant may be of significance to our understanding of human amniotic fluid embolism, and perhaps to our treatment of the condition.

Steiner and Lushbaugh[24] published observations involving the discovery of maternal pulmonary amniotic fluid embolism in 1941. At postmortem examinations they found microscopically disseminated occlusions of pulmonary arterioles and capillaries by debris from amniotic fluid. They correlated these findings with irreversible obstetrical shock of the patients. The embolic debris included meconium that had been discharged into the amniotic fluid by the fetus.[24, 25] The meconium debris included desquamated fetal epithelial cells, lanugo hairs, and vernix caseosa. These materials are normally accumulated as indigestible residue in the fetal gastrointestinal tract, as a cumulative result of drinking of amniotic fluid by the fetus, there to become stained by bile pigments and there to acquire addition of mucin. Steiner and Lushbaugh named the disorder amniotic fluid embolism, instead of meconium embolism, in order to allow for the possibility that significant embolism might sometimes arise from the debris of amniotic fluid alone, particularly from fluid rich in vernix caseosa, but without admixture of meconium into it. With animal experiments, they confirmed the view that the debris, rather than the amniotic fluid itself, caused the shock.

Beginning with the discovery of amniotic fluid embolism,[24] clinical findings led to the suggestion of some kind of a hemorrhagic tendency after the shock.[9, 24] Dooley and Leary[5] and Eames[6] eleven years later were the first to make observations which established that, during life, the circulating blood may become incoagulable as a result of amniotic fluid embolism. These investigators independently reported proved cases of amniotic fluid embolism[5, 6] in which the *venous* blood, collected during the stages of obstetrical shock, did not clot. From the experiments described in the following, it is indicated that a better understanding of this incoagulability phenomenon can be gained from con-

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trolled laboratory investigations. Even incoagulability of such blood after the addition of thrombin as described by Dooley and Leary[5] need not necessarily be interpreted as a demonstration of absence of fibrinogen.

Apparently actual measurements of fibrinogen, prothrombin, or Ac-globulin, or of anticoagulant concentrations have not been reported in human amniotic fluid embolism. An obstacle to obtaining such measurements is the difficulty of obtaining blood specimens for study. Not only is the disorder itself rare, but, in addition, it is acute and transitory in the sense that the patient is soon in extremis or recovered, and the fleeting opportunity for studies of blood coagulation quickly passes by during the urgency of the clinical problems associated with the obstetrical shock of the patient.

Methods

Meconium stools were obtained from newborn infants; occasionally a specimen had to be discarded because it appeared to be contaminated with feces. The meconium was suspended as a tenfold dilution in saline. The suspension was made by repeated, forceful aspiration and ejection from a syringe. Usually, simple centrifugation would not again separate a fluid layer from the particulate debris. For the present studies the meconium was injected rapidly, in single doses, intravenously into dogs under Nembutal anesthesia. Twenty-three dogs were studied and several additional animals were injected with meconium for related studies.

Venous blood was collected before and after the injections, using a two-syringe technique. Nine parts of blood were mixed with one part of 3.2 per cent sodium citrate in siliconed glassware. Plasma was obtained from the blood by centrifugation at 3,500 r.p.m. It was frozen and was later studied for activity of components of coagulation.

TABLE I. EFFECT OF MECONIUM INJECTION ON THE COAGULATION TIME AND ON THE PLATELET COUNT OF PERIPHERAL BLOOD. DOSES OF MECONIUM ARE GIVEN IN TERMS OF QUANTITY OF WHOLE, FRESH MECONIUM IN THE SUSPENSION INJECTED

MECONIUM MILLIGRAMS PER KILOGRAM BODY WEIGHT	LEE-WHITE COAGULATION TIME		PLATELETS, THOUSANDS PER CUBIC MILLIMETER		RESPONSE OF ANIMAL
	BEFORE	AFTER	BEFORE	AFTER	
Sublethal Doses.—					
110	27 minutes	4 hours	348	146	Respiratory distress
130	18 minutes	>20 hours	338	119	Shock, survived
Lethal Doses.—					
140	17 minutes	>20 hours	281	2.5	Died, 5 minutes
170	11 minutes	>20 hours	274	49	Died overnight
190			263	1.0	Died, 5 minutes
240	18 minutes	>20 hours	313	2.3	Died, 15 minutes
Supralethal Doses.—					
1,000	30 minutes	>20 hours	265	44	Died, 20 minutes
1,000	18 minutes	19 minutes	685	12	Died, 1 minute
1,400	30 minutes	6 minutes	422	4	Died, 1 minute

Fresh, whole blood was used for determinations of the Lee-White coagulation time. To minimize the volume of blood needed, yet still use a multiple-tube method, 0.5 ml. of blood was placed in each of 10 glass tubes of 6 mm. diameter. As can be seen in Table I, normal coagulation times were as long as 30 minutes. Similarly, 0.5 ml. quantities of freshly drawn blood were used for protamine titrations of a heparin-like inhibitor(s) of coagulation in an arithmetic dilution series equal to 0.02, 0.04, 0.06, 0.08, . . . 0.20 mg. of protamine

sulfate per milliliter of whole blood. This assay is based upon the observation of Chargaff and Olson[3] of the neutralization of heparin by protamine, and was performed in a manner comparable to that described by Allen and co-workers,[1] except that it was found necessary to examine the mixture for coagulation at intervals of a few minutes, by gentle tilting of the tubes. The end point was that concentration of protamine sulfate which gave a minimal coagulation time. In a similar manner, a series of dilutions of toluidine blue was also used to determine a "toluidine blue titer" on some of the specimens.

Platelets, including the individual platelets within clumps of them, were counted with the use of a phase contrast microscope, as in the counting chamber method of Brecher and Cronkite.[2]

Determination of fibrinogen was done by the method of Ware, Guest, and Seegers,[27] prothrombin by the method of Ware and Seegers,[26] and Ac-globulin by the method of Ware and Seegers.[28]

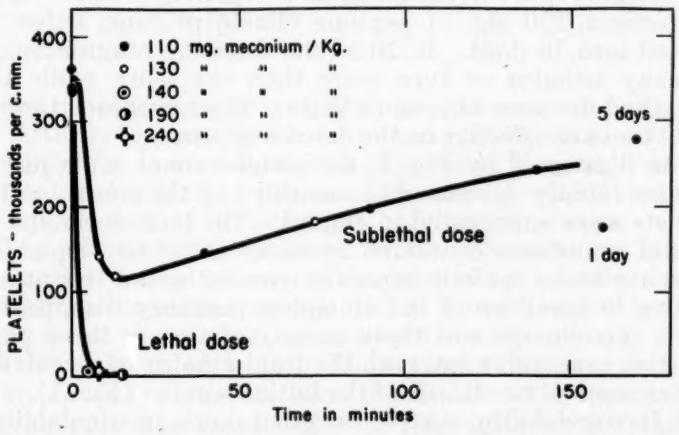

Fig. 1.—Experimental thrombocytopenia, and partial recovery from it, in dogs after sublethal intravenous injection of meconium. All platelets were counted, including the individual platelets within clumps of platelets. The thrombocytopenia was more severe with increasing dosage, being almost absolute after lethal doses.

Results

A. Lethal Doses of Meconium.—

When a dose of 1.4 ml. or somewhat more of meconium suspension, i.e., 0.14 ml. of meconium per kilogram of body weight, was injected rapidly into a leg vein of a dog, death usually occurred after a variable period in shock. The peripheral pulse became weak and thready and the respiration rapid. Debilitated or anemic dogs died quickly; healthy dogs frequently survived longer, or survived greater doses.

Venous blood, collected during the first half-hour after injection, usually had a Lee-White coagulation time of more than 20 hours; i.e., the blood failed to coagulate when allowed to stand in glass test tubes at room temperature (Table I).

Following the injections, the platelets all but disappeared from the circulation, less than 1 per cent remaining in venous blood (Table I and Fig.1).

Fibrinogen, prothrombin, and Ac-globulin remained in their normal concentrations in the plasma. Protamine titers were high, up to 0.06 mg. of protamine per milliliter of blood.

Postmortem Examination.—Neither in animals after ordinary lethal doses, nor in animals that were sacrificed after just sublethal doses, were there grossly visible fibrin deposits about the chordae tendinae of the heart or elsewhere. The blood did not coagulate in the heart or in the great vessels.

Microscopic examination of tissue sections confirmed the observations of Steiner and Lushbaugh[24] of disseminated pulmonary embolism of meconium debris; distribution of this embolic debris was restricted essentially to the pulmonary arterial and capillary tree. Squamous cells were prominent. With special stains, it was apparent that mucin caused much of the vascular occlusion; even with special stains no intravascular fibrin deposition was observed.

B. Just Sublethal Doses of Meconium.—

The retardation of coagulation was usually less severe than after lethal doses. The Lee-White coagulation time was prolonged several hours, or, indeed, in animals with profound shock, the prolongation was as great as after lethal doses, i.e., the blood failed to clot at all (Table I).

Comparison With Peptone.—The wet weight of meconium which caused severe shock in the dogs without causing death was 130 mg. per kilogram of body weight. Since the dry weight of the specimens, as collected, was 26 per cent of the wet weight, this corresponded to a dry weight of 33 mg. per kilogram. By comparison, 250 mg. of peptone (Bacto protone, Difco) per kilogram was injected into 16 dogs. In 10 of the dogs the coagulation time was prolonged by many minutes or even more than one hour, while the others showed a less marked decrease of coagulability. The meconium, therefore, was of the order of 10 times as effective as the dried peptone.

Platelets.—As illustrated by Fig. 1, the platelet count after just sublethal doses of meconium rapidly decreased to one-third of the control values. The remaining platelets were aggregated in clumps. The largest clumps tended to be cylindrical and sometimes contained as many as 30 to 40 platelets; only infrequently was a platelet entirely separate from at least a few others. Over an interval of two to three hours the clumping tendency disappeared; there were then only a few clumps and these usually of two or three platelets together. Within this same short interval, the total number of circulating platelets had again increased to two-thirds of the initial number (Fig. 1).

Duration of Incoagulability.—After sublethal doses, incoagulability usually developed somewhat more slowly than after lethal doses; it was maximal within less than one-half hour after injection of the meconium. Within approximately two hours, the coagulation time had again decreased to normal.

When there was extreme shock in surviving animals, comparable to the shock after ordinary lethal doses of meconium, complete incoagulability developed almost at once; this coincided with the acute thrombocytopenia, and preceded the maximal protamine titer.

Some Plasma Components of the Blood Coagulation Mechanism.—Despite the marked depletion of platelets, the failure of the blood to coagulate could not be attributed to a decrease of platelets alone because, in the surviving animals, the platelet depletion was partial, not complete, yet the incoagulability was sometimes extreme. Neither was the incoagulability caused by inactivation of, or by using up of, protein plasma components of coagulation.*

*In the assay for fibrinogen[27] it is customary to dilute the plasma thirty fold, then to add thrombin to obtain a fibrin clot which is later analyzed. In the present work the activity of the inhibitor became relatively unimportant at this dilution, and the fibrinogen assay could be performed. Even after the dilution, however, it was sometimes necessary to increase the amount of added thrombin by approximately fivefold, in order to coagulate the fibrinogen quantitatively.

The assay for prothrombin was more directly complicated by the circulating anticoagulant. In the assay for prothrombin,[28] it is necessary first to clot out the fibrinogen in order to avoid interference by it during the prothrombin assay. To accomplish defibrination in the specimens in which the anticoagulant effect was quite potent, the plasma was first treated with an appropriate amount of protamine sulfate. The protamine was added at the same time as the thrombin which was added to clot out the fibrinogen. After fibrin coagulation, removal of the added thrombin in the sense of essentially complete inactivation of it is necessary in order to avoid interference by the added thrombin in the subsequent measurement of the contained prothrombin.[28] This inactivation of thrombin proceeded adequately as usual, under the influence of the naturally present antithrombin.[23] Neither the heparin-like anticoagulant nor the added protamine sulfate seemed to interfere significantly with this or with the subsequent steps of the assay for prothrombin.

This is in contrast to the kind of depletion that sometimes occurs as a result of rapid initiation of intravascular coagulation in human abruptio placentae.[12, 15, 17-19] As can be seen in Table II, the concentrations of fibrinogen, of prothrombin, and of Ac-globulin in the blood remained normal after sublethal doses of meconium, just as they did after lethal doses. If there was any change at all, there appeared to be a slight tendency for an increase of these components of coagulation (Table II).

TABLE II.—CONCENTRATIONS IN FOUR SURVIVING DOGS, OF SOME PLASMA COMPONENTS OF COAGULATION. VENOUS BLOOD SPECIMENS COLLECTED ONE-HALF HOUR AFTER INJECTION OF MECONIUM SUSPENSION, I.E., DURING OR SOON AFTER SHOCK. THE VALUES ARE EXPRESSED AS PERCENTAGES OF THE LEVELS BEFORE INJECTION

DOG	FIBRINOGEN	PROTHROMBIN	AC-GLOBULIN
1	99	125	108
2	124	126	133
3	101	109	135
4	101	125	100

Despite its continued presence, fibrinogen was not always easily demonstrated. After severe shock, the undiluted plasma could not be caused to clot by the addition of bovine thrombin (Thrombin Topical, Parke, Davis & Co.) except in concentrations in excess of 20 units per milliliter of blood; i.e., in excess of approximately 40 units per milliliter of plasma. Coagulation could be caused by addition of thrombin in excess of 50 units per milliliter of plasma. Thus, the antithrombin activity of the plasma appeared to be unusually high. By first diluting the plasma several fold or by adding protamine sulfate, it was possible to make the plasma more sensitive to thrombin. The findings thus indicated that a powerful, heparin-like anticoagulant was present.

Protamine and Toluidine Blue Titrations.—The protamine titer in the surviving animals was occasionally as high as after a lethal dose, and this frequently reached levels of 0.06 mg. of protamine sulfate per milliliter of blood. If direct comparison with the results of Allen and associates[1] is permissible, this titer may correspond approximately to the presence of 0.06 mg. of heparin per milliliter of blood. In some of the surviving animals the coagulation times were prolonged only to several hours and the protamine titration method, as used, was not sufficiently sensitive to provide a definitive titration. In these, the prolongation of coagulation of the blood correspond approximately[1] to a level of 0.01 mg. of heparin per milliliter of blood.

The protamine titer reached its maximum within one-half hour after injection of meconium. After lethal doses of meconium, and with survival periods of the order of one-half hour or less, the protamine titer increased with the duration of the state of shock before death occurred.

The toluidine blue titer within the first half hour of shock, following a lethal or just sublethal dose of meconium, was approximately 0.015 mg. per milliliter of blood.

In the protamine sulfate titrations, but more especially in the toluidine blue titrations, the end points tended to be precise ones as though nearly exact proportions were required for neutralization of the anticoagulant. Higher concentrations, particularly of toluidine blue, inhibited coagulation for long periods.

Leukocytes, Hematocrit, and Erythrocyte Sedimentation Rates.—Following lethal doses of meconium the circulating leukocytes decreased acutely to one-fourth the control values. With sublethal doses, the leukopenia was less severe.

The hematocrit frequently increased during the shock of meconium embolism; in extreme cases in surviving animals this was as much as 10 points, e.g., from a hematocrit of 36 to 46 or from 42 to 52.

The dogs usually had high erythrocyte sedimentation rates. After the injection of meconium, whether of a lethal or of a sublethal dose, the sedimentation rates decreased to less than 1 mm. per hour.

C. Supralethal Doses of Meconium.—

Unusually large doses of meconium, approximately 10 times the lethal dose (Table I), were injected into 4 dogs. The effects upon the coagulation mechanisms were variable and, at times, opposite to those from lesser doses. Just as after ordinary lethal doses, the platelets almost entirely disappeared (Table I).

Shock and Death.—One of the 4 dogs survived for 20 minutes although shock was so profound that the peripheral pulse was not palpable except after direct exposure of the femoral artery. In this animal, the venous blood became incoagulable and the protamine titer was the highest observed, 0.09 mg. per milliliter of blood.

Immediate Death Without Shock.—The remaining dogs died at once after supralethal doses. Venous blood was collected two to three minutes after failure of respiration. The coagulability of the postmortem blood after such prompt death was variable. Blood from one of the 3 dogs had a normal coagulation time; the coagulation time of another was decreased from 25 minutes down to less than 6 minutes, while in the third it was prolonged to 40 minutes.

Postmortem Examination.—In contrast to the findings after ordinary lethal doses, within one-half hour after death there was coagulation of whole blood within the great vessels and within the chambers of the heart. This was postmortem coagulation and it occurred even in the dog of which the Lee-White coagulation time was prolonged to 40 minutes. There had been no separation of the blood into layers of erythrocytes and of plasma before coagulation. Microscopically there was much meconium debris in the pulmonary arterial tree and there was coagulation of whole blood as such.

D. In Vitro Mixing of Meconium With Blood.—

One part of meconium was mixed by agitation in glass test tubes with 9 parts of whole blood. The Lee-White coagulation time of this mixture was compared with the coagulation time of blood similarly mixed with one part of saline. With some specimens of meconium there was no effect on the coagulation time; by contrast, as noted by Steiner and Lushbaugh,[24] coagulation was sometimes greatly accelerated, a mixture with one specimen of meconium resulting in a decrease of the coagulation time from 16 minutes to 4 minutes; in no instance was there a prolonged coagulation time as in the in vivo experiments.

E. Experimental Therapy With Protamine Sulfate or With Toluidine Blue.—

In order to investigate whether the anticoagulant could be counteracted in vivo, protamine sulfate and toluidine blue were administered to dogs after they were given near-lethal doses of meconium. The dose of each drug was 0.5 mg. per kilogram of body weight. Four dogs were treated, two with protamine sulfate, two with toluidine blue. Administration of the drugs immediately after the meconium, or within one-half hour, did not seem to prevent or markedly to relieve the shock; each of the four animals developed a weak, thready femoral pulse and labored respiration; one of the two treated with protamine died overnight.

To the first dog, a pharmaceutical preparation of protamine sulfate for intravenous administration was given immediately after injection of the

meconium. A normal coagulation time was maintained and there was no measurable protamine titer within the first half hour or at the end of one hour. To the second dog the protamine sulfate was given at 25 minutes after the meconium embolism; within five minutes the coagulation time was reduced from more than 24 hours to a normal of 16 minutes. Within the same brief interval, the protamine titer was reduced from a high level of 0.06 mg. per milliliter of blood to a normal value of no measurable protamine titer.

To the third dog a pharmaceutical preparation of toluidine blue for intravenous administration was given immediately after the meconium embolism. This was without benefit to the coagulation system; the coagulation time of blood collected during the first half hour was longer than 24 hours and the protamine titer reached 0.05 mg. per milliliter of blood. To the fourth dog, toluidine blue from another source was made up and was given 20 minutes after the meconium embolism. The coagulation time of blood collected just before the administration of the toluidine blue was more than 24 hours but blood collected five minutes afterward had a normal coagulation time of 16 minutes. During the same time, the protamine titer disappeared. The "toluidine blue titer" of blood drawn just before the therapy with toluidine blue was 0.013; five minutes afterward it was reduced to a normal value of no measurable titer.

Comment

These experiments clearly show that incoagulability of the blood appeared after shock caused by meconium embolism, that although this may have been contributed to by depletion of platelets, it was not due to depletion of the components of coagulation from the plasma, and that a powerful anticoagulant was released into the circulation.

Shock and Release of Heparin.—Heparin is known to be released in peptone shock and in anaphylactic shock in laboratory animals.[11]

That the underlying mechanism responsible for the shock of meconium embolism may be different than that responsible for peptone shock or for anaphylactic shock is suggested by the classification of amniotic fluid embolism and of experimental meconium embolism as an "anaphylactoid" shock. By this term Steiner and Lushbaugh[24] understood that the underlying cause of the shock was the initiation of pulmonary arterial occlusion by minute and disseminated pulmonary embolism. From their observations, they concluded that the embolism itself was not the entire basis of the pulmonary circulatory occlusion, but that there was probably spasm of the pulmonary arterial tree as well. It is possible that such acute pulmonary arterial spasm may be mediated by release of a vasoconstrictor substance from platelets. The experiments above lend further plausibility to this interpretation because it was found that a considerable proportion of the platelets disappeared from the circulation and not all of them returned to it again (Fig. 1). If platelets had been lysed or damaged during agglutination or sequestration caused by the meconium injection, a vasoconstrictor such as serotonin from them could conceivably have been released locally or even into the general circulation. This possibility has not been investigated experimentally.

Extensive pulmonary arterial obstruction brought about by meconium embolism should lead to a most acute cor pulmonale. From observations of pulmonary and of systemic arterial pressures to be reported separately, it appears that such cor pulmonale may usually precede death in this kind of pulmonary arterial occlusion.

Even before the cardiac dysfunction of cor pulmonale could develop, the obstruction of the lesser circulation led to peripheral hypotension. When circulatory occlusion was so immediate and so complete as to lead to death

without an intervening period of survival, as, for instance, prompt death following the supralethal doses of meconium above, there was no detectable release of anticoagulant. This was similar to the failure of release of anticoagulant to occur in vitro. It appears then that shock invariably precedes release of the heparin-like anticoagulant.

Shock From Pulmonary Vascular Occlusion and Release of Heparin.—If shock following acute pulmonary occlusion during experimental meconium embolism is associated with release of an anticoagulant, as in the experiments above, then shock in other kinds of acute pulmonary vascular occlusion may conceivably also be associated with similar release of an inhibitor of blood coagulation. At least two conditions of shock which may be of the same kind as that of meconium embolism, but in which the occlusions are less sharply limited to the pulmonary vasculature, may be considered.

First, in separate experiments parallel to those of meconium embolism above, but not yet reported, shock followed transfusion of incompatible blood to dogs. As in the meconium embolism experiments, fibrinogen, prothrombin, and Ac-globulin concentrations were not altered, and more significantly, a large amount of heparin-like anticoagulant was released to the circulation.

Second, in the obstetrical shock of abruptio placentae, a residuum of incoagulability is sometimes found. The question may be raised whether an anticoagulant may be released. This state of hypocoagulability was referred to by Mellanby[14] and by Wooldridge as a "negative phase" of coagulation; they studied this in experimental animals when it followed the state of accelerated coagulation after intravascular injection of a potent initiator of coagulation. A marked degree of hypocoagulability under such conditions has been attributed to a depletion of the coagulation mechanism. There is depletion of fibrinogen.[14, 15, 17-19] That defibrination may occur in association with abruptio placentae or with eclampsia was observed by Dieckmann.[4] Depletion of components of coagulation other than fibrinogen also occurs[12, 15, 18] and, of these, as found by Johnson, Seegers and Braden,[12] Ac-globulin may essentially disappear. After the intravascular coagulation, not only may these components of coagulation be depleted, but a peculiar type of fibrin plugging can be found.[18] Conceivably it may be these fibrin plugs which initially cause the acute and severe shock which sometimes occurs in abruptio placentae.[18] From experimental observations to be reported separately, it is known that such fibrin plugging may be followed by increased pulmonary and decreased systemic blood pressure; in short, may be followed by shock comparable to that of the above meconium embolism. Conceivably, in this shock just as during the shock of meconium embolism, or of incompatible transfusion, an anticoagulant would be released into the circulation and this would tend to halt the generalized coagulation before absolute depletion of components of coagulation. Such a decrease of coagulability on the basis of release of an anticoagulant would be in addition to a possible hypocoagulability already caused by extensive depletion of the components of coagulation themselves. Evans,[7] in discussing the same general problem, concludes that "There is no reason why both of these explanations may not be true in part." His statement was prompted by his evaluation of the "negative phase" blood from injection of various initiators of coagulation, including thrombin, thromboplastin, and snake venom.[7] That some kind of anticoagulant, inhibiting at the level of conversion of fibrinogen to fibrin, may be indeed released during generalized intravascular coagulation has been demonstrated experimentally by Gerendas and Csapo.[8] These investigators observed a many fold increase of an antithrombin activity after shock caused by controlled injection of thrombin. They did not investigate as to whether their antithrombin-like activity was

due to heparin and it is not yet known whether their antithrombin, or perhaps complex of anticoagulants, may be the same as or different from the heparin-like anticoagulant that appeared in the experiments above. Their observations on experimental animals lend added significance to the possibility that release of an anticoagulant may play at least some role in the ultimate stages of acute disturbances of coagulation in abruptio placentae, and lead to the suggestion that appropriate, although difficult, measurements to detect release of anticoagulant might be of interest.

Inhibition Vs. Initiation of Coagulation in Amniotic Fluid Embolism.— Weiner and Reid,[29] Reid,[16] and Dooley and Leary[5] postulate that the blood may become incoagulable in human amniotic fluid embolism as a result of intravascular coagulation. Consistent with this possibility, it has been demonstrated in the rabbit, a particularly sensitive animal, that intravascular coagulation, as demonstrated by histologically visible fibrin deposition, could be induced by rapid injection of clarified amniotic fluid,[17] provided that large volumes, 30 ml. or more, are given. The lethal volume for ordinary, non-clarified amniotic fluid, when not contaminated with meconium or with decidual tissue juices, was almost as large.* The large volume was required because the content of thromboplastin was only of the order of 1 mouse unit per milliliter of amniotic fluid.[17] During late human pregnancy, it can be estimated by comparison with results in experimental animals and by allowing for an increased sensitivity during pregnancy that, on the basis of the inherently contained thromboplastin, the lethal dose of amniotic fluid would be of the order of 500 to 900 ml. Although little is known with certainty of the exact path of entry of amniotic fluid into the maternal circulation, there would seem to be some problem raised by a requirement of such a volume of amniotic fluid to be released into the maternal circulation quickly. Hence, in the proposed view of Weiner and Reid[29] it would seem necessary to invoke an additional source of thromboplastin or some other potent substance capable of initiating blood coagulation. Thus far, not only is there no recorded demonstration of depletion of fibrinogen, prothrombin, or Ac-globulin in amniotic fluid embolism, but there has been no demonstration by fibrin stains or by other suitable means of the presence of fibrin deposits, or of fibrin formation and the lysis of the fibrin as a result of amniotic fluid embolism.

Finally, were it not for the findings of blood coagulation after injection of *supra*lethal doses of meconium into the above dogs, and were it not for the report of Hemmings[10] of the unique observation of the pathologist Rafael Dominquez of "fibrin thrombi" after the death of a woman by amniotic fluid embolism, the above conclusions might seem to be complete, namely, that the disturbances of coagulation caused by meconium embolism are caused by an inhibition of coagulation. However, after the unusually large doses of some specimens of meconium, intravascular coagulation was observed; the peculiarity of this coagulation was that it occurred only in dogs which died instantly. This agonal or postmortem coagulation was like the in vitro acceleration of coagulation which could be caused by mixing certain specimens of meconium with freshly drawn blood (above) and it is possible that the same mechanism, whatever that may have been, may have caused the test-tube coagulation and the acute postmortem coagulation. These observations lend pertinence to the question of whether some kind of "fibrin thrombi" might occasionally be found in human maternal amniotic fluid embolism, particularly if the patient died instantly, or almost instantly, as did the patient of Hemmings.[10] Because these seemingly anomalous observations of coagulation after acutely supralethal doses

*Results of investigations carried out during a residency in obstetrics and gynecology at Woman's Hospital, Detroit, 1949.

of meconium provide a plausible mechanism for an occasional observation of "fibrin" or of "thrombi," it becomes unnecessary to postulate that intravascular coagulation should be the primary cause, or even a significant contributing cause, of incoagulability in amniotic fluid embolism, in the sense of depletion of components of the coagulation mechanism, as has been sometimes postulated.[16, 29]

These studies have shown that the release of anticoagulant into the blood stream during experimental meconium embolism may be so great as to permit a refractory response to any but massive doses of added thrombin, without fibrin formation. This is similar to the observations in the case of Dooley and Leary,[5] that "A gross test with bovine thrombin failed to produce fibrin . . ." and the lack of coagulation in that case could have been the result of inhibition and/or inactivation of the added thrombin. Unless this possibility can be excluded, the conclusion that defibrination occurred[5] will remain unproved. A less equivocal fibrinogen assay[27] or a fibrin titer assay based on a dilution series[21] should be helpful in detecting and in measuring fibrinogen in such cases. A significant observation is provided by the completeness of the incoagulability of the whole blood in the case of Dooley and Leary and in the case of Eames, by contrast, defibrinated blood, either from animals[15, 17] or from patients with abruptio placentae, [4, 12, 15, 17, 18] usually coagulates, even though defibrination is relatively severe and even though the coagulum may sometimes be a tenuous one, or may soon lyse again.[15, 16, 18] From analysis of appropriate specimens of blood, it should be possible to determine directly whether the incoagulability of blood of amniotic fluid embolism may be actually due to an anticoagulant.

Limitations of Therapy With Protamine Sulfate or With Toluidine Blue.— If during amniotic fluid embolism incoagulability should become a problem by contributing to hemorrhage, a question may arise as to the advisability of therapy with protamine sulfate or with toluidine blue as an adjunct to obstetrical management, to counteract the supposed anticoagulant.

If there were a risk due to uncertainty of diagnosis as to whether the patient had some different, chief disturbance of coagulation, such as fibrinopenia or defibrination acutely acquired during abruptio placentae, then use of these drugs might be unwarranted and dangerous because of their own anticoagulant effects.[22]

Even with a manifest hemorrhagic tendency and an apparent clinical diagnosis of amniotic fluid embolism, there are still limitations to the practicality of this therapy. Toluidine blue is said to be too slow in its action to be useful in vivo in acute conditions[22] and, therefore, if either drug were to be used, the preference would probably be for protamine. In addition, the neutralization of heparin-like activity, especially by toluidine blue, proceeds according to rather definite proportions[22] and, in the test tube at least, these drugs of themselves, when in excess, tend to render the blood incoagulable or hypocoagulable; hence in therapy it would seem to be desirable to estimate the precise dose closely. For this reason it would be necessary to obtain a protamine titer before treatment in order to administer the drug with assurance of deriving benefit from it and to minimize the risk of harm by overdosage with a considerable possibility of thereby inadvertently increasing difficulties of coagulation. If available, a more rapid, although more complex, method of protamine titration such as that of LeRoy, Halpern, and Dolkart[13] would be helpful in obtaining a titer quickly enough to aid in decisions of therapy. These problems are inherent in treatment of acute incoagulability with protamine sulfate or with toluidine blue.

The possibility of a transitory nature of the incoagulability must be considered; in the above experimental animals, at least, the period of incoagulability was maximal for only one-half hour, and probably of significance

only during the first hour; the coagulation time had returned to normal within two hours. The question might be raised whether in a patient with a presumably certain diagnosis of amniotic fluid embolism, the condition of incoagulability may become self-limiting before the appropriate dose of protamine could be determined, or whether there might be some risk of the protamine effect outlasting that of the heparin-like anticoagulant; under such conditions, the therapy itself might perhaps contribute somewhat to a continued hemorrhagic tendency by its own anticoagulant activity.

Hence, it would seem that therapy with protamine sulfate would be indicated only if the diagnosis of amniotic fluid embolism could be made early enough and with conviction sufficient to warrant such a bold course of treatment. The dosage should be estimated on the basis of a protamine titration of a specimen of the patient's blood.

Summary

After experimental injection of meconium suspensions into animals, the blood became incoagulable. There was a marked decrease in the platelet count but this alone was not adequate to render the blood incoagulable. Neither was the incoagulability secondary to inactivation of, or using up of, important plasma components of coagulation, for these remained in normal concentration. Instead, a powerful, heparin-like anticoagulant was found in the circulating blood. The observations lead to the conclusion that this anticoagulant was released into the circulation during shock. In view of the experimental findings and of recent reports in the literature of indefinite prolongation of the coagulation time in two proved cases of human amniotic fluid embolism, it is possible that release of an anticoagulant may occur in association with the shock of maternal amniotic fluid embolism. Such an anticoagulant could play a major role in the obstetrical hemorrhage which sometimes appears to be a complication of amniotic fluid embolism.

Addendum.—While this paper was in press, an interesting report by Ratnoff and Vosburgh,[30] of another patient with proved amniotic fluid embolism, and with certain studies of coagulation of venous blood, has appeared. "Three and a half hours after the appearance of the symptoms of shock, there were signs of a generalized hemorrhagic state. The patient's blood appeared to be incoagulable. This clotting defect was associated with hypofibrinogenemia, excessive plasma thrombin-inhibitory activity, slight thrombocytopenia and increased plasma fibrinolytic activity."

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REVIEW OF THREE HUNDRED FIFTY-THREE CASES OF PREMATURE SEPARATION OF THE PLACENTA

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ONE of the most serious accidents and complications of pregnancy is the premature separation of the placenta. The catastrophe has been labeled variously. DeLee called it placental abruptio. Holmes used the term placentae ablatio, while Couvelaire expressed it as uteroplacental apoplexy. The term now used and listed in the *Standard Nomenclature of Diseases,* as used for chart coding in approved registered hospitals, is "premature separation of the normally implanted placenta due to unknown causes." It is wise and desirable to report the percentage of separation, as well as to indicate to a certain degree the severity of the separation. Although the amount of separation is an important index of the severity of the accident, it alone is not always the determining factor in the outcome of the condition. As shown later, a stillborn fetus may be delivered with only a 3 per cent separation and a living child delivered with a 100 per cent separation.

Kimbrough and Jones[1] reported an incidence in a twelve-year period with 113 cases of 1:250 deliveries. Barrett[2] in 1945 reported an incidence of 1:150 to 1:200. Over a ten-year period between 1942 and 1952, the incidence of premature separation at Charity Hospital was 1:226. The Charity Hospital incidence thus coincides fairly well with that quoted.

Over this ten-year period, 353 premature separations were encountered in a total of 79,972 deliveries, a percentage of 0.44. The first five years from 1942 through 1946 produced 27,501 births and the second five-year period, from 1947 through 1951, yielded 52,471 deliveries. The percentage of separation, interestingly enough, was almost identical, namely: 0.47 and 0.42, or 129 and 224 cases, respectively.

When figures relating to incidence between white and Negro races were checked, it was found that, in the last eight years and five years, respectively, the white to Negro admissions were 1:5.5. The ratio of separations of white to Negro for the last five-year period was 1:4.2. It is thus seen that the incidence of premature separation was slightly higher in the white than in the Negro race. In percentages, the white race had 0.51 per cent separations and the Negro race had 0.41 per cent separations.

Dorsett[3] in 1945 stated that the incidence was higher in primiparas; the series at Charity did not substantiate this, however. Of the 353 premature separations in the ten-year period, 79, or 22 per cent, occurred in primiparas and 274, or 78 per cent, occurred in multiparas; 49.5 per cent in gravidas i to v, and 28.5 per cent in gravidas vi or more The highest was para xiii, gravida xviii; she had a premature separation for the first time at 36 weeks' gestation. This patient, like many others of the 353 , had several previous early abortions. In reality it is difficult to say whether some early abortions are or are not premature separations of the placenta and, thus, many of the so-called first sepa-

rations may truly not be the first. Likewise, premature separation may be considered an abortion or threatened abortion. To quote DeLee, "A premature separation is in reality an abortion near, or at term."

The age groups were investigated and it was interesting to find that the highest incidence occurred in the third decade of life, which coincides with the age group of highest incidence of procreation as well as the optimal period. In the 20 to 29 year period of the respective five-year groups the incidence was 53.49 per cent and 52.57 per cent. The next highest incidence was in the 30 to 39 year age group—29.46 per cent and 21.87 per cent, respectively. Table I gives the respective decades and percentages for the two five-year groups.

TABLE I

DECADE (YEARS)	1942-1947	1947-1951
14-19	13.95%	17.86%
20-29	53.49%	52.57%
30-39	29.46%	21.87%
40-49	3.10%	6.70%

The Charity Hospital has three separate functioning services. Two are connected with two different Medical Schools and Staff, and the third is a non-school service. Each service thus functions with different policies and procedures, making interservice observations and comparisons highly educational and instructive. I will, therefore, at times compare the various services regarding statistics, procedures, and results. The two school services are allotted 40 per cent of the patients each and the third service 20 per cent. I shall designate the two school services A and B and the other service C.

Maternal Deaths

It is interesting to note that there were a total of four maternal deaths over the ten-year period and all four occurred in the last two years, two deaths in each year. The percentage was 1.1 per cent. Kimbrough and Jones[1] reported a maternal death rate of 1.8 per cent and, in 1945, H. E. Harvey[4] reported 14 maternal deaths out of 293 cases, or 4.8 per cent. Services A and B suffered two deaths each and both had a mortality in each of the last two years. Following is a brief summary of each case, stressing only the pertinent facts.

CASE 1, Service A.—The patient, L. E., was a Negro woman, 36 years of age, para ix, gravida x, at term. This was her first premature separation. The fetal heart tones were not heard, there was external bleeding, and the uterus was hard. She was in labor, with pain in the abdomen, severe eclampsia, and shock. The blood pressure was 80/40, pulse 28, respirations 40, edema two plus. Nausea and vomiting were present. There was progressive uterine enlargement, the membranes were intact, and the cervix dilated 2 cm. Upon admission the presenting part was found to be at station minus 4. Due to the serious condition of the patient and her poor progress with a diagnosis of probable Couvelaire uterus, a low transverse section and hysterectomy were performed. A Couvelaire uterus with complete separation and a stillborn infant were found at operation. The patient died due to severe eclampsia and the placental separation complication. Postmortem examination showed liver necrosis and kidney damage.

CASE 2, Service A.—The patient, B. K., was a Negro woman, 20 years of age, para 0, gravida i, at term. The fetal heart tones were not heard. She was not in labor. The uterus was hard with progressive enlargement and nausea and vomiting were present. She had eclampsia, with convulsions seven hours prior to admission. On admission, a right transverse lie was found, and a low transverse cesarean section was elected. Hysterectomy was done after operation revealed a Couvelaire uterus with complete separation and a dead fetus. On the first

postoperative day urinary output was 12.5 c.c.; blood urea nitrogen was 133. Section was done on April 19, 1951. The patient had secondary closure of the operative wound and had a severe convulsion on May 10, 1951. She died May 11 with a diagnosis of cerebral thrombosis and eclampsia. Postmortem was not obtained.

CASE 3, Service B.—The patient, C. B. F., was a Negro woman, 33 years of age, para viii, gravida ix, at 36 weeks' gestation. This was her first premature separation. The fetal heart tones were heard, there was external bleeding, and a soft uterus. She was in labor three days after admission. She had eclampsia with hypertensive renal vascular disease, the cervix was not dilated, and the vertex was at station minus 4. The patient delivered from below a live baby. The percentage of separation was not reported. Blood pressure before delivery was 200/150 with 3 plus albumin and 4 plus edema. Service B has a policy of hydrating eclamptic patients with large volumes of hypertonic dextrose solutions. In this case, post delivery, the patient received a total of 12,610 c.c. as intravenous fluids, the output was 3,707 c.c., and she went into cardiac failure, which was apparently the primary factor in her decease. This might well be considered an avoidable death.

CASE 4, Service B.—The patient, M. G., was a 38-year-old Negro woman, para iv, gravida v, at 34 weeks' gestation. The fetal heart tones were not heard. There were external bleeding, a hard uterus, and pain. The patient was in labor, with eclampsia. On admission, the blood pressure was 220/130, albumin 4 plus, and edema 3 plus. The service elected to allow the patient to continue in labor and deliver from below. The fetus was stillborn with 40 per cent separation of the placenta. The patient died with congestive cardiac failure.

Infant Salvage

Cosgrove and Conway[5] in 1941 reported a total fetal mortality of 58.6 per cent. In the discussion of this paper, Cosgrove, reporting on another series of 51 cases, quoted a fetal mortality of 33 per cent.

In the ten-year period under discussion at Charity, there were 211 live babies and 149 stillborns. Subsequently, ten of the 211 died. The 211 live babies accounted for 59.7 per cent of the total. Corrected to number of babies actually salvaged, the percentage is 56.9 per cent. The stillborn babies accounted for 40.3 per cent.

Of these 211 babies born alive, the fetal heart tones could be heard in only 162. Thus the fetal heart tones in 49 were not heard. This brings out a very important point, namely, that, although there appears to be no remaining sign of fetal life, one should not hesitate to treat the patient as if the baby were alive. Many of these babies were delivered by cesarean section and, had operation been postponed, many of these infants might have died. These 49 actually represented 23.4 per cent of the infants born alive.

Duration of Gestation

The duration of gestation was investigated to see if any certain period of gestation might be more prone to premature separations. The ten-year period was again divided into two five-year periods. Two significant factors were revealed. The two different periods are tabulated in Table II, indicating the number of separations for each week of gestation.

The first thing noticeable on examination of Table II is that the greatest number of separations unquestionably occur at term. This could be explained by the fact that the placenta is mature and is ready for delivery of the fetus and its own third stage, thus needing very little stimulation toward separating from the uterine wall. Therefore, any stimulating factor, whether chemical or physical, as toxemia, hypertension, fetal movements, sudden rupture of membranes, falls, etc., may cause a premature separation of the placenta.

TABLE II. DURATION OF GESTATION

1942-1946		1947-1951	
WEEKS	NO. CASES OF SEPARATION	WEEKS	NO. CASES OF SEPARATION
18	1	18	0
19	1	19	0
20	2	20	0
21	0	21	0
22	4	22	1
23	0	23	1
24	8	24	14
25	0	25	1
26	0	26	4
27	1	27	0
28	12	28	16
29	0	29	1
30	7	30	9
31	1	31	2
32	8	32	13
33	0	33	6
34	2	34	6
35	0	35	9
36	13	36	30
37	3	37	10
38	5	38	14
39	7	39	16
40	47	40	64
41	4	41	2
42	2	42	0
43	0	43	0
44	1	44	0
?		?	5
Total	129	Total	224

The other point of interest is that premature separation is most prone to occur, and did occur in this series of cases, at the end of each lunar month of gestation. Upon examination of the histories, definitely greater numbers of separations are seen to have occurred in the twenty-fourth, twenty-eighth, thirty-second, thirty-sixth, and fortieth weeks. These periods apparently coincide with the time of cyclic changes that occur in the nonpregnant woman during the physiological hormonal variations and endometrial changes.

With this knowledge in mind, it might be wise to treat parturient women with abortion tendencies conservatively with bed rest and possibly hormone therapy at and around these crucial periods of gestation, with extra caution at term.

These figures are significant since each five-year period shows the same marked change at the end of each lunar month.

Percentage of Separation

Compilation of the percentage of separation, Table III, indicated that the greatest percentage of catastrophes and fetal deaths occurred with separations of 30 per cent or more. Fortunately, over 50 per cent of all the separations occurred below the 40 per cent separation group. The highest percentage of fetal mortality occurred with 70 per cent or more separation. The lowest percentage of separation with fetal death was 3 per cent; death of the infant was here due to excessive blood loss and anoxia of the fetus in utero.

On the other extreme, the records revealed four cases of living babies being born with 100 per cent premature separation. The patients lost very little blood and anoxia was a very minor factor as the separations occurred during the second stage of delivery, the placentas being delivered with the baby.

TABLE III

PERCENTAGE OF SEPARATION	1942-1946		1947-1951		10 YR. TOTAL		PERCENTAGE OF SEPARATIONS RESULTING IN FETAL DEATH
	NO.	DEAD	NO.	DEAD	NO.	DEAD	
1-9	6	0	29	5	35	5	14.2%
10-19	12	1	20	2	32	3	9.3%
20-29	11	1	21	4	32	5	15.6%
30-39	3	2	17	7	20	9	45.0%
40-49	1	1	6	3	7	4	57.1%
50-59	2	2	10	6	12	8	66.6%
60-69	2	2	4	2	6	4	66.6%
70-79	2	2	2	2	4	4	100.0%
80-89	0	0	2	2	2	2	100.0%
90-99	3	3	9	7	12	10	83.3%
100	19	18	44	41	63	59	93.6%
Marginal	9	2	6	1	25	3	12.0%
?	47	5	57	20	104	25	24.0%

The 100 per cent separations in the ten-year series outnumbered all of the other percentages of separation and many occurred at or near term.

Treatment

Tables IV, V, VI, and VII give us information regarding the pertinent factors of the cesarean sections and their results.

The second five-year period showed a slight increase in the number of sections done. The ratio of separations in the two each five-year periods was 1:1.7, whereas the ratio of sections between the first five-year and the second five-year period was 1:2.1. The increase in sections done was mainly by Service A. This service became more radical in the second period. Service B showed their usual conservatism, in fact, they became more conservative since they had only one more section in the second period, even though the number of separations almost doubled. Service C, on this basis, also became much more conservative since only one section was done for a separation of the placenta.

TABLE IV. CESAREAN SECTION STATISTICS

	NO. OF SECTIONS	FETAL HEART TONES		LOW CERVICAL	LOW TRANSVERSE	LOW VERTICAL	LOW CERVICAL UNCLASSIFIED	UNCLASSIFIED	CLASSICAL	LIVE	DEAD	HYSTERECTOMY	
		PRESENT	ABSENT									TOTAL	SUBTOTAL
1942 to 1947	19	8	11	12	1	9	2	2	5	6	13	4	
1947 to 1952	37	12	26*	28	10	13	5	1	8	17*	21	4	4
1942 to 1952	56	20	37	40	11	22	7	3	13	22	34	12	

*One above number of sections due to one set of twins.

The indications for sectioning the patients with premature separation of the placenta were essentially the same for all services, namely, unripe cervices, or cervices relatively ripe and partially opened, but with poor mechanism of labor where time was a precious factor. The severity of the separation as shown by hard uterus, shock, and excessive blood loss was also an important

TABLE V. INDICATIONS FOR SECTION

SERVICE	NO. OF SECTION	DILATATION OF CERVIX	STATION	MEMBRANES: INTACT	MEMBRANES: IN LABOR	COUVELAIRE UTERUS	% SEP.	PARITY	HYSTERECTOMY	SEVERE SEPARATION
1942-1946.—										
A	6	2 1 cm. 2 2 cm. 2 3 cm.	3 floating 1 0 2 ?	4	4	4	2 90 1 100 3 ?	1 primipara 5 multiparas	3	1
B	6	5 0 cm. 1 3 cm.	3 floating 3 3	6	5	1	1 90 1 100 4 ?	3 primiparas 3 multiparas	1	0
C	7	3 0 cm. 2 2 cm. 1 3 cm. 1 4 cm.	7 floating	6	3	2	4 100 1 75 1 50 1 ?	1 primipara 6 primiparas	1	1
Total 19										
1947-1951.—										
A	29	3 0 cm. 7 1 cm. 10 2 cm. 4 3 cm. 1 4 cm. 4 ? cm.	12 floating 3 3 3 2 2 1 1 0 8 ?	23	14	16	13 100 2 90 3 50 1 60 1 25 1 20 1 3 7 ?	12 primiparas 17 multiparas	9	5 2
B	7	1 0 cm. 3 1 cm. 3 2 cm.	6 floating 1 ?	7	2	2	4 100 1 20 2 10	2 primiparas 5 multiparas	4	0
C	1	1 0	1 floating	1	0	0	1 30	1 primipara	0	0
Total 37										

TABLE VI. CESAREAN SECTION VERSUS DELIVERY FROM BELOW

	1942-1946		1947-1951		1942-1951	
	NUMBER	%	NUMBER	%	TOTAL NUMBER	%
Vaginal delivery	110	85.3	187	83.5	297	84.5
Section	19	14.7	37	16.5	56	15.8
Hysterectomy	5	3.8	13	5.8	18	5.7
Section, live babies	6	31.6	16	43.2	22	25.4
Section, dead babies	13	58.4	21	56.8	34	74.6

factor. There were cases, however, in which Service B would attempt delivery per vaginam, whereas Service A would employ section.

Thus we see from Table VII that Service A went from 22 per cent sections and 78 per cent conservative deliveries per vagina to 31.8 per cent sections and 68.2 per cent conservative deliveries. Live babies by section increased from 16.6 per cent to 34.4 per cent and live babies by vaginal delivery rose from 50 per cent to 62.9 per cent.

TABLE VII. TYPE OF DELIVERY PER SERVICE

SERVICE	TYPE OF DELIVERY	1942-1946 NO.	%	LIVE BIRTHS	%	1947-1951 NO.	%	LIVE BIRTHS	%
A	Section	6	22	1	16.6	29	31.8	10	31.4
	Vaginal delivery	20	78	10	50	62	68.2	39	62.9
B	Section	6	7.3	4	66.6	7	6.7	3	42.8
	Vaginal delivery	76	92.7	63	82.8	97	93.3	60	61.8
C	Section	7	31.8	1	14.2	1	3.7	1	100
	Vaginal delivery	15	68.2	8	53.3	26	96.3	15	52.6

Service B on the other hand (Table VII) practically remained stationary as regards percentage of sections and conservative deliveries per vaginam, but the fetal salvage rate dropped in both section babies and conservative delivery babies. Section salvage dropped from 66.6 per cent to 42.8 per cent and conservative delivery salvage dropped from 82.8 per cent to 61.8 per cent.

Service C decreased the section rate from 31.8 per cent to 3.7 per cent and increased conservative deliveries from 68.2 per cent to 96.3 per cent with an increase in the fetal salvage rate in both from 14.2 per cent to 100 per cent in section and 53.3 per cent to 57.6 per cent in deliveries per vaginam.

Perhaps Service B could improve its fetal salvage rate by more prompt sectioning and pursuing a more radical policy.

Although Service B's salvage rate seems to have suffered by its conservatism, one must admit that its salvage percentages are still in the same range as those of the other services and notwithstanding Service A's apparent improvement, Service B's section salvage rate is still higher than that of Service A.

Apparently, one must reach a happy medium as regards procedure of treatment, for choice of radical or conservative treatment depends on experience and the situation at hand. As seen from the table discussed, both radical approach and conservatism have their advantages and rewards as well as disadvantages and pitfalls.

Tables V and VI revealed five hysterectomies and thirteen hysterectomies in the respective five-year periods. These were done mainly because of Couvelaire uteri. Twelve out of eighteen hysterectomies were done because of Couvelaire uteri, the other six apparently because of high parity. Ten mild Couvelaire uteri were encountered and left in, and the patients recovered without undue difficulty.

The total number of sections was 56, or 15.8 per cent of the 353 cases of premature separation. The percentage of live births resulting from sections in the ten-year period was 37.5, 33.5 per cent for the first five years and 39.4 per cent for the second five years.

It will be noted by checking Table V that low cervical sections increased in incidence and that they have come into their own in the second five years as compared to the first five years. It will also be noted that in the last three years, when hysterectomies were indicated, total hysterectomies were done when the patient's condition permitted rather than subtotal hysterectomies. This is a commendable trend toward better obstetrical management.

Toxemias of Pregnancy

During the study of this ten-year series of premature separations of the placenta, it became quite evident at a relatively early time that the toxemias of pregnancy were associated with premature separations quite frequently and apparently were an important factor in their occurrence.

There were a total of 133 cases with toxemia of pregnancy, or 37.6 per cent of the 353 cases of separation of the normally implanted placenta. One hundred nineteen, or 89.4 per cent, were pre-eclampsia, 9, or 6.7 per cent, were eclampsia, and 18, or 13.5 per cent, were hypertensive renal diseases. Some of the latter had pre-eclampsia superimposed on them and were included in the above-mentioned 119 cases.

The majority of these patients delivered spontaneously per vaginam, with artificial rupture of membranes used to advantage whenever possible. Of these 133 cases, Pitocin induction was used in 14, or 10.5 per cent; Service A, 2 cases, B, 9 cases, and C, 3 cases, respectively. Twenty-nine patients, or 21.7 per cent, were delivered by cesarean section; these accounted for 51.7 per cent of all cesarean sections.

Table VIII gives the number of radical and conservative treatments per service with their respective outcomes. Statistically, the conservative mode of therapy yielded the highest fetal salvage. It must, however, be remembered that the cases in which section was used were usually of greater severity and thus would give lower fetal salvage rates. Besides, maternal salvage almost always is an important factor to consider and value also.

TABLE VIII. TREATMENT AND OUTCOME BY SERVICES

	SERVICE A	%	SERVICE B	%	SERVICE C	%	TOTAL	%
Sections.—								
Live babies	4	21	3	42.8	2	66.6	9	31
Stillborn	15	79	4	57.2	1	33.4	20	69
Conservative management.—								
Live babies	12	40	28	46.6	6	42.8	46	44.2
Stillborn	18	60	32	53.4	8	57.2	58	55.8
Total	49		67		17		133	
% of total toxemias		36.8		50.4		12.8		100

Pitocin

It was seen above that cesarean section was resorted to mainly in severe cases in which the cervix was not ripe and dilating or in which no labor was in progress with the same type of cervix, especially in primiparas and in some severe cases of low parity with only slight progress in labor.

The opposite type of cases, those which were mild, with cervix ripe, and labor in good progress, especially cases of prematurity, were allowed delivery from below or at least an attempt at such delivery.

Pitocin was used in 11.9 per cent, or 42 cases, over the entire ten-year period. A number of the Pitocin inductions were used as a supplement to accomplish a more rapid delivery in an attempt to raise the infant salvage rate and also to ward off excessive blood loss or development of a Couvelaire uterus.

Strangely enough, there was a tendency to decrease the number of Pitocin inductions in the second five-year period. The last three years of the first five-year period saw the introduction of Pitocin and first usage was in individual subcutaneous doses every half hour. In the second five-year period, the Pitocin was introduced into 1,000 ml. of dextrose water solution. The amount given depended upon the response of the patient. During the first five-year period 14 per cent of the patients were given Pitocin, whereas in the second five-year period 10 per cent of the deliveries were Pitocin induced.

Its use was especially adapted and desirable in cases of premature babies with placental separation where rapid delivery was most desirable and extra effort seemed proper to keep the mother from becoming an obstetrical cripple.

Signs, Symptoms, and Findings

Ten important signs and symptoms were recorded that were characteristic of premature separation of the placenta. One very important sign, namely, hyperirritability of the uterus, was noted so infrequently that I did not record this sign, believing a true picture would not be presented.

The signs and symptoms will be presented according to the frequency in which they were found.

Premature separation occurred in 294 cases out of 353 when the patient was in labor. Thus 83.2 per cent of the cases occurred in patients who were in labor. This seems to be very logical, as it would seem more probable for a placenta to become detached from a contracting moving base than it would from one that was quiescent and not contracting.

The next factor in order of highest frequency which suggested separation of the placenta prematurely was external bleeding. Two hundred ninety-two cases, or 82.7 per cent, of all the premature separations had frank external bleeding and 17.3 per cent had occult bleeding. The external bleeding occurred anywhere from forty hours to just prior to delivery of the fetus at the end of the second stage. The amount of bleeding or blood loss was likewise a variable factor and, as might be surmised, the greater the amount lost, the more serious were the consequences for both infant and mother. The quantity of blood lost ranged from a few to 2,000 c.c.

Next in line of frequency and of fair importance, but not completely foolproof, was the absence or presence of fetal heart tones. Out of 211 liveborn babies, fetal heart tones were heard in 162 cases; thus 76.7 per cent of the living babies were known to be alive through the hearing of the baby's heart, while 23.3 per cent were feared to be dead. Thus, we can say that, if fetal heart tones are heard, we can be assured the baby is living, but if not heard the baby is not necessarily dead and if the fetus is of viable age one should attempt to complete delivery as quickly as possible. Only in this way will the highest fetal salvage be possible.

Fetal movement was present in less than one-third of the entire series and proved less reliable than presence of fetal heart tones. Only 105, or 49.7 per cent, of liveborn babies were found to have active fetal movements by either the patient's own consciousness or by the operator's palpation.

Pain did not occur with as great a frequency as expected. Out of the entire group 118, or 33.4 per cent, of the women complained of pain. The pain varied from a mild to severe backache and from a mild to severe "tearing" type of sensation within the abdomen. One patient gave a history of experiencing a moderately severe abdominal pain several days prior to onset of labor and spontaneous delivery from below.

In 104 cases hard uteri were felt by the palpating hand. A point of interest and of importance is that the greater the percentage of separation, the more liable is the uterus to be hard and the harder it will be. It is quite obvious then that, the harder the uterus, the more severe and serious the case will be, and action toward a rapid delivery should not be delayed. The percentage of Couvelaire uteri is likewise high and they are found primarily in these cases.

Shock is usually to be expected in the severe cases of premature separation. Thirty-seven cases, or 10.4 per cent, presented a picture of shock. Fifty-nine and four-tenths per cent of the patients in shock were in labor when first seen. All except one developed shock prior to delivery. Rupture of the membranes at times may precipitate shock, as occurred in one case.

Another sign characteristic of premature separation of the placenta is a progressive enlargement in size of the uterus. This, naturally, is due to the free bleeding into the uterus without the discharge of much or any of the blood through the vagina. There were only twenty-nine cases, 8.2 per cent of the total, where mention was made of this important factor. I am certain there were many more cases than recorded, but this sign is difficult to obtain from nonobservant patients and difficult for the physician to determine since he unfortunately usually is not in attendance from the onset of the condition. This may, however, be suspected to have occurred when large amounts of blood clots are expelled at the end of the second and third stages.

Nausea and vomiting were found in association with premature separation of the placenta in only ten of the most severe cases. One case was terminal and combined with severe eclampsia. From this experience, then, a serious case must be anticipated when nausea and vomiting are present.

There are certain severe cases which may or may not be, but usually are, associated with pre-eclampsia or eclampsia that develop a bleeding tendency. This is brought about by a fibrinogenopenia, which directly affects the normal blood-clotting mechanism. This is usually effectively combated by administration of fibrinogen directly intravenously or by transfusions of freshly drawn blood which in itself contains fibrinogen. In the series of premature separations under discussion, there were four cases of fibrinogenopenia reported. One patient received 1 unit of fibrinogen intravenously with complete recovery. The other three were given fresh whole-blood transfusions. Two of the four had section hysterectomies and died. The other recovered without further incident.

Miscellaneous Factors

Trauma.—Trauma is usually emphasized in the minds of laymen and in a good many textbooks as the cause of premature separation of the placenta. True, trauma, when severe enough, may incite a premature separation, but the incidence as found in this series did not show trauma as a prominent cause of separation.

There was a total of 15 cases, 4.2 per cent of the 353 cases, caused by trauma. The types of trauma are interesting and instructive, 40 per cent being directly the result of manipulation during the attendants' examination or procedure.

The following causes were found to account for the traumatic separation of the placenta:

One patient developed bleeding and onset of pain while coughing.

Five patients gave histories of falling in one fashion or another. One patient fell down a flight of stairs, twelve feet, and another just tripped over a step.

One patient developed bleeding and pain a few hours after coitus.

Another patient stated she developed sudden pain and bleeding while lifting a tub of wash.

Two patients developed bleeding following rectal examination. These had low-lying placentas.

One patient developed a premature separation of the placenta during an attempted external manual rotation of the fetus while another did so during a manual rotation from left occipitoposterior to left occipitoanterior.

One patient developed a premature separation twenty-four hours following a transabdomino-intrauterine tap for relief of polyhydramnios.

One patient developed a sudden separation after a severe tetanic contraction, following the initial induction injection of 0.5 ml. of Pitocin.

One case was listed under trauma since it was considered to be caused by a mechanical factor and thus, in a sense of the word, traumatic in nature. This was in a patient with a large leiomyomatous uterus.

Umbilical Cord.—The umbilical cord played a part in six of the 353 cases. Two of the accidents resulted in stillbirths, while the remaining four had a happier outcome with deliveries of living infants.

Two of the cords were simply short and produced a 95 per cent and 50 per cent separation, respectively, with the first one producing a stillbirth and the other one a live baby.

One cord had a true knot in it with a 25 per cent separation.

One baby was stillborn with the cord wrapped tightly around the neck; another cord with two loops around the baby's neck caused 10 per cent separation, but did not take the infant's life.

A 15 per cent separation was caused by the cord being looped around both legs of the live infant.

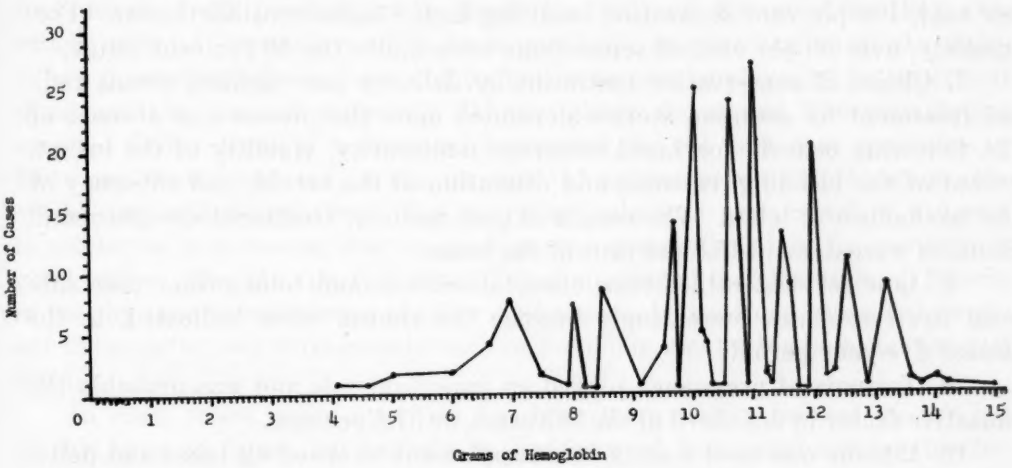

Fig. 1.

Hemoglobin Factor.—The 353 separations were grouped against the hemoglobin values of the patients. From Fig. 1, it will be noted that the greatest number of separations occurred at the level of 11 Gm. of hemoglobin. It will also be noted that the number of cases of separation decreases more rapidly as the hemoglobin value rises and drops sharply after 13 Gm. hemoglobin is reached, though this is only 2 Gm. of hemoglobin above 11 Gm. The decrease in number of separations in the other direction toward increasing anemia, however, is much slower; there were roughly half again as many cases of separation among the anemic patients as among the normal.

It may be said, then, that anemia increases the incidence of premature separation. This indicates that proper diet and proper maintenance of blood-forming elements would help in decreasing the incidence of premature separation of the normally implanted placenta.

Summary

1. Three hundred fifty-three cases of premature separation of the normally implanted placenta out of 79,972 deliveries over a ten-year period in the Charity Hospital of New Orleans have been reviewed and an incidence of 1:226 deliveries has been reported.

2. Premature separation was found slightly more frequent in the white than in the Negro race and was much more frequent in multiparas than in primiparas, 78 per cent and 22 per cent, respectively. Fifty-three and five-tenths per cent of the cases occurred in the 20- to 29-year age group of parturient women.

3. The maternal death rate was 1.1 per cent, a total of four cases, all occurring in the last two years of the survey.

4. Two hundred eleven babies were liveborn, 149 stillborn; 10 babies died postnatally, giving a corrected fetal salvage rate of 56.9 per cent and a stilllbirth rate of 40.3 per cent.

5. Premature separations were found to be more likely to occur at the termination of each lunar month of gestation, and were most frequent at term. This observation makes ultraconservative treatment advisable at these periods.

6. Greatest incidence of fetal death occurred in separations of over 30 per cent, 100 per cent separation resulting in the highest stillbirth rate. Fortunately, over 50 per cent of separations were under the 40 per cent range.

7. Choice of conservative treatment by delivery per vaginam versus radical treatment by cesarean section depended upon the presence or absence of the following criteria for rapid delivery: multiparity, viability of the infant, extent of the bleeding, ripeness and dilatation of the cervix, and efficiency of the mechanism of labor. The results of each mode of treatment are discussed. Sections were done in 15.8 per cent of the cases.

8. Low cervical rather than classical sections and total rather than subtotal hysterectomies increasingly become the choice, when indicated, in the second five-year period.

9. Toxemia of pregnancy played an important role and was probably the causative factor in one-third of the 353 cases, or 37.6 per cent.

10. Pitocin was used mainly as a supplement to speed up labor and delivery, the intravenous drip method being used in the last five-year period.

11. The various signs and symptoms of premature separation of the placenta were listed according to frequency and discussed.

12. Miscellaneous factors and their significance are discussed in relation to traumatic and anatomical causations of premature separation of the placenta.

13. It was found that anemia in the patient played an important role as the incidence of separation was greatest in the more anemic patients.

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INTRAVENOUS PITOCIN INFUSION IN LABOR

A Report of 100 Consecutive Cases

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THE use of posterior pituitary extract in labor prior to the birth of the child has been widely condemned by most obstetrical teaching centers in the past four decades. As pointed out by Reid[1] in 1946 and Eastman[2] in 1947, this rather universal attitude resulted from unreliable standardization of the drug, its use in relatively large doses, and its indiscriminate employment in obstetrical situations which would ordinarily dictate against the use of labor-stimulating agents. Today there is widespread agreement on the fact that oxytocics in labor are contraindicated in the presence of cephalopelvic disproportion, abnormal presenting part (brow, face, scapular), placenta previa, lack of progress in dilatation and descent despite good uterine contractions, and in patients of great parity. Despite this, it is generally acknowledged that Pituitrin or Pitocin in the first and second stages of labor continues to be used and abused throughout the country, not infrequently with unfortunate results for both mother and child.

In more recent years attention has been more widely focused on the use of this drug in labor, particularly in instances of functional uterine inertia. One of the major stumbling blocks up to the present has been the questionable efficacy of the various modes of administration of Pituitrin and Pitocin. Hofbauer[3] suggested the use of intranasal Pituitrin by means of cotton pledgets soaked with the drug and inserted into the patient's nares. This method has proved to be unreliable because of the variation in the rate of absorption in different individuals. The most popular method of administration has been the intramuscular injection of minute quantities (0.5 minim to 1.0 minim) of the drug at regular intervals of 20 minutes or more. Both Reid[1] and Eastman[2] have cautiously advocated this method as a valuable one in the treatment of uterine inertia. However, they too have placed emphasis on the fact that the amount of drug in the blood stream cannot be definitely regulated and consequently the outcome is unpredictable.

Theobald[4] in Great Britain and Hellman,[5] Scadron,[6] and Stone[7] in this country were among the first to report success with the dilute intravenous drip method of administration. These workers have used dilutions ranging from 1:500 to 1:10,000 at rates of several drops to 2 c.c. per minute, with rather good results. Hellman, Harris, and Reynolds,[8] in a study of the contractility patterns of the uterus stimulated by dilute intravenous Pituitrin drip, concluded

that the intravenous method gave better tokodynamometric patterns and far greater physiological increase in work gradient than the intramuscular method. That the uterus should work in a more regular and physiological manner with the intravenous mode of administration is to be expected. The amount of drug in the blood stream at any one time is constant and can be easily regulated by adjustment of the rate of flow or dilution, with consequent elimination of the individual variation in the rate of absorption.

It is our belief that intravenous Pitocin used carefully and under strict supervision allows for a safe and efficient means of using posterior pituitary extract during the first and second stages of labor. Indiscriminate and careless use of this method will lead to disastrous results and discredit a technique which we feel is a valuable contribution to the obstetrical armamentarium.

Methods and Material

During the past three years the intravenous drip of Pitocin or Pituitrin has been used in almost 1,000 cases at the Beth Israel Hospital. During this period of time we have noted no serious sequelae directly attributable to this method of using posterior pituitary extract. One hundred consecutive cases in which intravenous Pitocin was used as a means of either inducing or aiding labor were chosen for intensive study. They were selected without consideration of indication for use or the type of labor prior to its use, and closely followed during labor. It was impossible to include the patients delivered prior to the beginning of this study due to the fact that many of the pertinent data required could not be obtained from their charts.

Fifty nulliparous and fifty multiparous (para i, 40 cases; para ii, 8 cases; para iii, 2 cases) patients were studied. Of these, there were forty-six attempted inductions of labor and fifty-four patients received intravenous Pitocin as a means of stimulating labor already in progress. Before the flow of Pitocin was started, measures were taken to assure the fact that there was no disproportion present, either by clinical examination, x-ray pelvimetry, or both.

The patients were usually sedated prior to the start of the infusion. Women already in labor had received sedation consisting of 100 to 125 mg. of Demerol, 0.4 mg. of scopolamine, and 0.1 to 0.2 Gm. of Seconal at about 3 to 4 cm. dilatation. The patients in whom labor was induced or who were not in active labor received the same sedation thirty to sixty minutes prior to the start of the drip. Sedation was then repeated as indicated.

We prefer the use of Pitocin rather than of Pituitrin. Our reasons for this preference are as follows:

1. The avoidance of the vasopressor effect of Pituitrin.[9]
2. The avoidance of the vasospastic effect of Pituitrin on the coronary arteries.[10]
3. The avoidance of the simultaneous use of cyclopropane anesthesia and Pituitrin.[11, 12, 13]

On several occasions where the induction of labor had failed with Pitocin, we were successful when Pituitrin was substituted. Whether this was due to the Pituitrin per se or to the fact that the preceding bottles containing Pitocin had better "ripened" the cervix, we cannot say.

A dilution of 7½ minims of Pitocin in 500 c.c. of 5 per cent glucose in water or saline (1:1,000 dilution) was found to be very satisfactory. There has been noted no difference in the results whether glucose in water or saline was the diluent. On occasion as little as 2 minims in 500 c.c. of solution has been

used with good results. After the infusion is started and allowed to run at a rate of 10 to 12 drops per minute, the Pitocin is added to the flask and thoroughly mixed. Early in our experience it was noted that allowing the infusion to run at a more rapid rate at the start was frequently the cause of tetanic uterine contractions. The method now used avoids the administration of a sudden large amount of Pitocin which is the cause of the prolonged severe contractions. After about thirty minutes the rate of flow is gradually increased to about 20 to 30 drops per minute. When necessary (i.e., with weak, irregular contractions despite a slow drip of Pitocin), the infusion is allowed to run as fast as 60 to 80 drops per minute. Usually, however, when the uterus does not respond adequately to a slow drip, increasing the rate of flow does not seem to improve the contractions appreciably.

During the entire period of Pitocin administration it is necessary to follow the fetal heart beat carefully, especially during the first hour immediately following the start of the infusion. There is occasionally noted a persistent increase of uterine tone and, not uncommonly with it, a slowing of the fetal heart beat shortly after the start of the infusion. This is readily corrected by temporarily discontinuing the infusion until at least 20 to 30 minutes after the fetal heart rate has returned to normal. The infusion can then be restarted at a very slow rate of flow and gradually increased to the desired speed. Rarely, a tetanic contraction will be noted several hours after the start of the Pitocin.

We allow the Pitocin drip to run continuously until well after the end of the third stage of labor. Immediately after the delivery of the placenta the rate of flow is increased to 60 to 100 drops per minute. This technique is at variance with that reported by Stone[7] and Labate and Barbaro[14] who permitted the solution to run only until caput was visible or until the cervix was fully dilated and delivery seemed desirable.

Results

The Use of Pitocin to Aid Labor Already in Progress.—

There were 54 patients studied in whom intravenous Pitocin was used as a means of stimulating uterine contractions after the patients had been in labor for varying periods of time. Satisfactory results were obtained in all but 2 cases. The average duration of the first stage of labor in 34 nulliparous women was 14 hours and 24 minutes (high 30 hours; low 3 hours, 20 minutes). The length of time in labor before the Pitocin drip was begun averaged 10 hours and 45 minutes (high 24 hours, 3 minutes; low 2 hours, 30 minutes). The time required after the start of the infusion until full dilatation averaged 3 hours and 38 minutes (high 13 hours, 45 minutes; low 15 minutes). The average duration of the second stage of labor was 49 minutes (high 2 hours, 4 minutes; low 10 minutes). The third stage of labor averaged 7 minutes (high 20 minutes; low 2 minutes).

In the group of 20 multiparous women the first stage of labor averaged 9 hours and 12 minutes (high 26 hours, 45 minutes; low 2 hours, 30 minutes). Prior to the beginning of the infusion the average time in labor was 8 hours and 6 minutes (high 22 hours; low 1 hour, 20 minutes). After the start of the Pitocin the time required until full dilatation was reached was 1 hour and 6 minutes (high 4 hours, 45 minutes; low 10 minutes). The second stage of labor averaged 17 minutes (high 35 minutes; low 5 minutes) and the third stage 12 minutes (high 1 hour, 34 minutes; low 1 minute) (Table I).

The response provoked by the infusion had no relationship to the degree of cervical dilatation at the time the drip was begun. Those patients with slight cervical dilatation responded as readily and as rapidly as those women with a greater cervical dilatation.

TABLE I. LENGTH OF LABOR

	NULLIPAROUS, 34 CASES	MULTIPAROUS, 20 CASES
A. The Average Duration of Labor in Patients Aided With Pitocin.—		
First Stage:		
Average	14 hours, 24 minutes	9 hours, 12 minutes
High	30 hours	26 hours, 45 minutes
Low	3 hours, 20 minutes	2 hours, 30 minutes
Second Stage:		
Average	49 minutes	17 minutes
High	2 hours, 4 minutes	35 minutes
Low	10 minutes	5 minutes
Third Stage:		
Average	7 minutes	12 minutes
High	20 minutes	1 hour, 34 minutes
Low	2 minutes	1 minute
B. The Average Length of Labor Before Pitocin Started.—		
Average	10 hours, 45 minutes	8 hours, 6 minutes
High	24 hours, 30 minutes	22 hours
Low	2 hours, 30 minutes	1 hour, 20 minutes
C. The Average Length of First Stage After Pitocin Started.—		
Average	3 hours, 38 minutes	1 hour, 6 minutes
High	13 hours, 45 minutes	4 hours, 45 minutes
Low	15 minutes	10 minutes

The length of labor after the onset of the Pitocin drip did not appear to be influenced by the condition of the membranes (ruptured or intact) at the time the infusion was started. Full dilatation was arrived at as rapidly in patients whose membranes were intact when the Pitocin was started as in those patients whose membranes were ruptured at that time.

Considering all 54 cases, an average of 242 c.c. of the Pitocin solution was required until delivery of the baby (high 600 c.c., low 20 c.c.).

From the data obtained it can be seen that once the intravenous flow of Pitocin was begun labor was brought to a relatively rapid termination. The average length of labor for this group of cases is not much shorter than the average standards for normal labor; however, our figures are distorted by the prolonged labors of a large number of patients with uterine inertia. The quality of the labor improved almost immediately after the start of the infusion. Regular, strong uterine contractions occurring every two to four minutes and lasting forty-five to sixty seconds were noted. The labors were clinically identical to normal, strong, physiological labor.

The indications for the use of intravenous Pitocin to aid labor already in progress are listed in Table II, *A*.

TABLE II. INDICATIONS FOR THE USE OF INTRAVENOUS PITOCIN

A. Aided Group.—		*B. Induction Group.—*	
Elective use	24 cases	Elective induction	23 cases
Primary uterine inertia	18 cases	Ruptured membranes	9 cases
Secondary uterine inertia	9 cases	Pre-eclampsia	5 cases
Persistent rim of cervix	2 cases	Discomfort of patient	5 cases
Pre-eclampsia	1 case	Postmaturity	3 cases
		Prediabetes	1 case

Of the 24 patients who electively received a Pitocin drip good results were obtained in all but 2 cases. Both of the latter patients were nulliparous women on whom a Pitocin infusion had been started about three hours after the onset of labor. There was 3 and 4 cm. cervical dilatation when the infusions were started. Both patients had been having mild contractions every eight to ten minutes before labor was stimulated. Contractions began occurring every three

to five minutes but were of only moderate intensity. Thirteen and fourteen hours, respectively, were required until full dilatation was reached. This elective group in toto was in labor an average of five hours before the infusions were started (high 11 hours; low 1 hour, 20 minutes). The first stage of labor was then terminated in an average of 2 hours and 30 minutes (high 14 hours; low 10 minutes). In all but the 2 cases described, labor progressed to a rapid and normal termination. These results prove only the already known fact that normal physiological labor can be further stimulated to a more rapid termination with the use of oxytocics. No serious ill effects were observed in this group.

Eighteen women with primary uterine inertia were treated with a Pitocin infusion. We have employed Eastman's[9] definition of primary uterine inertia, which is labor characterized from the onset by feeble contractions of short duration occurring at long intervals, and resulting in undue delay in progressive dilatation of the cervix. Labate and Barbaro[14] reported 75 per cent success in the management of their group of patients. All 18 of our patients responded satisfactorily. The patients were in labor an average of 13 hours and 40 minutes before therapy was started (high 24 hours; low 7 hours). Once the infusion was started, full dilatation was reached in an average of 3 hours and 10 minutes (high 7 hours, low 1 hour). The response was quite dramatic. We have since noted several cases of primary uterine inertia which have not responded satisfactorily to the use of Pitocin. Two women (observed after completion of this series) with primary inertia who were given Pitocin over prolonged periods of time and who did not respond adequately were noted to have pathological uterine retraction rings at the time of cesarean section. It is felt that in those patients already in labor who do not respond adequately to Pitocin, the persistent use of the drug is dangerous. If the response is not adequate we recommend not using more than 500 c.c. of a 1:1,000 solution over a minimum of four hours.

The use of intravenous Pitocin provides very gratifying results in the management of secondary uterine inertia. We again used the definition given by Eastman[9]: a labor which began in a typical manner with promise of an ordinary speedy termination, but which, without appreciable cause, comes to an apparent standstill with contractions coming less frequently and intensely. At the same time, the cervix, which was becoming obliterated and dilated in a satisfactory manner, ceases to make further progress. Pitocin was usually started after a halt in the progress of labor of two to three hours. Excellent results have been reported by Hellman and co-workers,[8] and Labate and Barbaro.[14] Our findings are in agreement with those given in the literature. We treated only 9 patients with secondary inertia. The average length of labor prior to the start of the infusion was 16 hours and 12 minutes (high 24 hours, 26 minutes; low 11 hours, 25 minutes). Following the start of the Pitocin, full dilatation was reached in an average of 2 hours and 12 minutes (high 6 hours, 30 minutes; low 15 minutes). In six of the 9 cases, full dilatation was reached within one hour. All the patients responded rapidly and without complication.

Two women received intravenous Pitocin in conjunction with a saddle block to facilitate dilatation of a persistent rim of cervix. Both patients were having good labor and had a persistent thick rim of cervix for more than two hours. Full dilatation was reached within 30 minutes in both cases. Since the completion of this series, we have used this combination on many occasions with excellent results. The relaxation of the perineal floor, paravaginal tissues, and circular muscle fibers of the cervix, together with the enhanced contractions stimulated by the drip, allows for rapid dilatation of the cervical rim and descent of the fetus. This method is certainly preferable to an attempt at delivery through a cervix which is not completely dilated.

Induction of Labor.—

There were forty-six attempts at induction of labor. The indications are listed in Table II, *B*. Successful induction was accomplished in 42 patients and failed in 4, a failure rate of 9 per cent. There were 16 nulliparous and 26 multiparous women studied. Induction was successful in all sixteen nulliparous women. The 4 failures occurred in the multiparous group of patients.

Certain criteria must be met before one can be reasonably assured that success will be achieved. The most important factor is the "ripeness" of the cervix —the effacement, consistency, thickness, dilatation, and position of the cervix. Ideally, we look for a completely effaced, thin (1 cm. or less), soft cervix that is located anteriorly and is at least 2 cm. dilated. Where these criteria are found, it is rare to fail with an attempted induction. Exceptions are naturally seen, and one such case will be described later.

The condition of the amniotic sac is of importance. Women with ruptured membranes can almost invariably have labor rapidly induced with Pitocin. While it is well known that rupture of membranes alone will usually be followed by labor, the use of the Pitocin solution hastens the onset of this process. We have frequently seen patients remain in the hospital for several days leaking amniotic fluid, and only after the start of a Pitocin drip have they gone into labor. Conversely, with patients making no progress with the infusion alone, rupture of the membranes has hastened the onset of labor. We do not artificially rupture membranes, however, unless the vertex is filling the inlet well.

The time at which progressive cervical dilatation or effacement was first noted was considered to be the time of onset of labor. Rectal examinations were done every fifteen to thirty minutes after the start of the infusion. If cervical changes were noted, the time of the last examination was considered the point of onset of labor. We did not feel that the onset of uterine contraction should be used to determine this point, for in almost all cases (even 3 of the 4 failures), contractions began soon after the start of the infusion.

In 29 cases labor began within thirty minutes after the start of the infusion. In 27 of these cases the cervix was "ripe," but in 2 patients the cervix was 1 cm. dilated, thick, and not completely effaced. Membranes had ruptured prior to the start of the infusion in both of the latter patients. In 6 cases labor did not begin for forty-five minutes to one hour. All patients in this group had "ripe" cervices. A lag of two to four hours was noted in 4 patients. All 4 women in this group had cervices that were 1 cm. dilated, thick, but effaced. Two of these women had ruptured membranes before the infusions were started. Two patients did not respond to the first attempts at induction but induction was successful the following day in one case and two days later in the second case, after prolonged latent periods. Both women had cervices which were not properly "ripened" and intact membranes. One patient received 500 c.c. of solution over a three-hour period without success. Several hours later contractions began spontaneously and the Pitocin was restarted. Labor then progressed normally. As expected, the "riper" the cervix, the shorter the latent period observed. Except in a few isolated instances, the patients with thick, posterior, not completely effaced, undilated cervices required a longer latent period before labor began. These findings also tend to indicate that, not infrequently, when the cervical criteria mentioned above are not met, the persistent use of the Pitocin infusion will lead to success of induction.

The average amount of Pitocin solution (1:1,000) required in the lag period before the onset of labor was 145 c.c. (this figure is distorted somewhat by 2 women who received 1,250 c.c. and 1,500 c.c.). The average amount of solution required from the time of onset of labor until delivery of the baby was 145 c.c.

In all 18 cases in which membranes were ruptured, induction was successful. We were not able to make any correlation between the condition of the membranes (ruptured or intact) at the start of the induction and the length of the lag period before labor began.

The average duration of the first stage of labor in 16 nulliparous patients was 5 hours and 30 minutes (high 12 hours. 30 minutes; low 1 hour, 40 minutes). The second stage lasted an average of 52 minutes (high 3 hours, 4 minutes; low 13 minutes) and the third stage 7 minutes (high 33 minutes; low 2 minutes). The 26 multiparous women averaged 2 hours and 20 minutes (high 5 hours, 45 minutes; low 45 minutes) for the first stage of labor, 19 minutes (high 1 hour, 4 minutes; low 2 minutes) for the second stage, and 5 minutes for the third stage of labor (Table III).

TABLE III. THE AVERAGE DURATION OF LABOR IN PATIENTS IN WHOM LABOR WAS INDUCED WITH PITOCIN

	NULLIPAROUS, 16 CASES	MULTIPAROUS, 26 CASES
First Stage:		
Average	5 hours, 30 minutes	2 hours, 20 minutes
High	12 hours, 30 minutes	5 hours, 45 minutes
Low	1 hour, 40 minutes	45 minutes
Second Stage:		
Average	53 minutes	19 minutes
High	3 hours, 4 minutes	1 hour, 4 minutes
Low	13 minutes	2 minutes
Third Stage:		
Average	7 minutes	5 minutes
High	33 minutes	19 minutes
Low	2 minutes	1 minute

In 3 of the 4 cases in which we met with failure of induction the cervix was thick, firm, not effaced, and only 1 cm. dilated. The cervix in the fourth case was 4 cm. dilated, soft, effaced, and anterior. In the latter patient no change was noted in the cervix after 250 c.c. of solution had been given despite the fact that she had regular contractions of fair quality. Of the 3 patients with "unprepared" cervices, one progressed from 1 to 4 cm. dilatation and then made no further progress. The cervix also became effaced during this time. (This was the one exception to the criteria used for determining the time of onset of labor.) After several hours at this dilatation the cervix began to become thicker and edematous and the infusion was discontinued. The second woman had regular contractions but there was no effacement or dilatation of the cervix over a three-hour period (200 c.c. used). The third patient developed no contractions during the entire time that 500 c.c. of solution was running. Membranes were intact in all four women.

Blood Loss.—

The average estimated blood loss for the 96 deliveries was 236 c.c. There was no estimated blood loss over 700 c.c. In 21 per cent (20 cases) of our series, a postpartum relaxation of the uterus was noted immediately following the termination of the third stage of labor. In all instances this was successfully controlled by further injections of Ergotrate or Pitocin, uterine massage, or by restarting the infusion if it had been discontinued prior to delivery.

A definite increase in postpartum atony was noted when the infusion was discontinued prior to delivery of the placenta. In the 96 cases studied, the infusion was discontinued prior to the end of the third stage of labor 41 times. Twelve of the 20 cases of uterine atony occurred in this group. It is to be noted, therefore, that 30 per cent of the patients whose infusions were discontinued prior to the end of the third stage of labor developed uterine atony.

In 55 cases the infusions were continued for varying periods of time after delivery of the placenta. Eight, or 15 per cent, of this latter group of women developed postpartum atony. Uterine atony, therefore, occurred twice as often in the group of women whose infusions were prematurely discontinued. Observation since has confirmed these findings.

Effect on Blood Pressure and Pulse.—

A recording of the blood pressure and pulse of each patient was made just prior to the start of the infusion, after the infusion had been running for one hour, and after delivery of the placenta. No effect on either the blood pressure or pulse was noted as a result of the prolonged intravenous drip of Pitocin.

Unusual Cases.—

Seven of the cases studied presented unusual features. Two patients with twin pregnancies received intravenous Pitocin—labor was induced in one and aided in one with Pitocin. Labor progressed uneventfully in both women. After the delivery of the first baby a diagnosis of the presentation and position of the second twin was made, so that Pitocin would not be continued in the presence of an abnormal presentation. The postpartum blood loss was average in amount. One patient with rheumatic heart disease was given a Pitocin drip to shorten the duration of her labor. No complications were noted and we have since used a Pitocin infusion on several patients with cardiac disease. It appears to be of great value in shortening the length of the first and second stages of labor. One woman who had had a previous myomectomy received Pitocin intravenously to stimulate labor. Labor and delivery were uncomplicated. A fifth patient with multiple fibroids received a Pitocin drip without ill results. Two patients were studied in whom there existed some doubt as to the adequacy of the midpelvis for the passage of the fetus. Labor was desultory in both women. A Pitocin infusion was started with the feeling that both women deserved an adequate trial of good labor before cesarean section was contemplated. One woman had an interspinous diameter of 9.4 cm. and a posterior sagittal of the midpelvis of 3.8 cm. Architectural features were good except for slightly convergent sidewalls. The baby was estimated to weigh 6 to 6½ pounds. After the start of the infusion labor progressed rapidly and normally and a 6 pound, 4 ounce, baby was delivered without difficulty. The second patient had a pelvis with good measurements but poor architectural features. The baby was estimated to be 8½ to 9 pounds in size. Labor, here also, progressed rapidly and normally after the start of the infusion, and a 9 pound baby was delivered by low midforceps operation.

Complications.—

Three women developed tetanic uterine contractions after the start of the Pitocin drip. In all 3 cases, the contractions developed soon after the Pitocin solution entered the blood stream. In two of these patients the fetal heart rate dropped to 60 and 92 beats per minute while it remained normal in the third case. The contractions persisted for 2½ to 3 minutes and subsided after the infusions were discontinued. The fetal heart beats also returned to normal after the infusions were discontinued. In all 3 women, the infusions were restarted at a very slow rate of flow after 30 minutes, and gradually increased in rate. Normal babies were subsequently delivered. It appears significant that all 3 cases occurred among the first 6 women studied in our series.

One baby (weight 7 pounds, 8 ounces) suffered a depressed fracture of the right frontal bone. The baby was delivered by forceps rotation and extraction from right occipitoposterior position. It is felt that the fracture was sustained during the process of delivery. The frontal bone was elevated surgically and

the baby was discharged in good health. One patient had an adherent placenta which was retained for 1 hour, 34 minutes, until removed manually. It is difficult to ascribe either of these complications to the use of the Pitocin infusion.

There were no fetal or maternal deaths in this series.

Conclusions

1. The intravenous administration of Pitocin by dilute infusion is a safe and efficient means of stimulating labor when properly controlled.

2. Its use gives excellent results in the treatment of primary and secondary uterine inertia. It is felt that this method of therapy will radically and safely alter the management of these cases.

3. Intravenous Pitocin used on patients already in labor considerably shortens the average duration of labor. Patients in whom labor is induced also have labors which are much shorter than the average standards.

4. The use of the Pitocin infusion in conjunction with saddle block anesthesia is suggested as a possible means of therapy for patients with a persistent rim of cervix. Further trial with this method is merited.

5. Intravenous Pitocin provides an efficient means of induction of labor. The most important considerations for success are "ripeness" of the cervix and rupture of the membranes. In properly selected cases failure of induction is a rare occurrence.

Conversely, the rate of failure is related to the percentage of unprepared cervices. Persistent use of the Pitocin will, however, cause a certain percentage of these patients to go into labor. Its use in this fashion is not recommended.

6. The Pitocin infusion should be allowed to run until well after the completion of the third stage of labor. Failure to do so will lead to a rise in the incidence of postpartum uterine atony.

7. Intravenous Pitocin used over a prolonged period during labor has no effect upon the blood pressure and pulse of the mother.

8. The continued use of the Pitocin drip in cases of uterine inertia that do not readily respond is contraindicated. Persistent use in these cases is dangerous.

We should like to express our deep gratitude to the Obstetrical Attending Staff of the Beth Israel Hospital for allowing us the privilege of using many of their private cases for this study.

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THE ROLE OF ADRENALIN (EPINEPHRINE) IN LABOR AND THE USE OF AN ADRENOLYTIC DRUG TO PREVENT POSTPARTUM HEMORRHAGE

Observations Based on 3,500 Cases

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IT IS not yet clear what initiates labor, nor why the contractions occur at long intervals at first, then become more frequent, stronger, and last longer. Once labor has started, we presume that the uterus responds to the oxytocic action of the posterior pituitary gland producing the contractions of the uterus, and we assume that the relaxation phase results when the posterior pituitary hormone is not acting. That is, the contractions are produced by the positive action of posterior pituitary hormone, while the relaxation is considered as a negative phase of the same force. This cannot explain why the uterus does not continue to stay contracted after it has attained that state. We believe there must be an active positive force which stimulates the uterus to relax. That a mechanism of contraction and relaxation is essential to physiological labor is taken for granted; it is necessary for the retraction of the uterine muscle fibers, the dilatation of the cervix, and the expulsion of the fetus.

We had to find what it is that stimulates the uterus to relax. Consideration had to be given to the motor functions of the uterus, to the central nervous sysem, to the extrinsic nerves acting on the uterus, to the intrinsic nerves; also to the sympathetic and parasympathetic nerves; and to the action of Adrenalin, noradrenalin, and acetylcholine. Much has been written on the physiology of the uterus, but there is no explanation of how the relaxation of the uterus occurs during labor.

In 1927, Rucker[11] had shown that when performance of a version was interfered with by tight contraction of the uterus in labor, the uterus could be relaxed by giving a small dose of epinephrine, showing that epinephrine (Adrenalin) stimulated the uterus to relax. We have frequently seen patients who were in active labor at home, whose pains would cease on admission to the hospital. The explanation for this is that the emotional excitement upon entering the hospital causes an excess secretion of epinephrine which counteracts the uterine contractions. From these observations, we inferred that epinephrine is an active force in labor, and that it is this substance which stimulates the sympathetic nerves to relax the uterus. There is, therefore, the oxytocic action of the posterior pituitary producing the contractions of

the uterus, and the endogenous epinephrine causing the relaxation of the uterus, thereby maintaining the physiology of labor. This process continues until the cervix is fully dilated, and the fetus is delivered.

After the baby is born the uterus contracts down, the placenta is immediately detached from the uterine wall and is ready to be delivered. The uterus having contracted down should stay contracted; however, frequently it does not remain so, but relaxes again. This condition is attributed to exhaustion of the uterine muscle fibers as a result of a long labor, and is designated as secondary uterine inertia. This explanation would hold if the uterus had remained distended and failed to contract at all, but having contracted it should stay that way and not relax again.

Our explanation for this relaxation is that the uterus continues to go through the process of contraction and relaxation the way it does in the first and second stages of labor. During the first and second stages of labor this mechanism is normal and desirable, but after the third stage it is no longer desirable and is harmful, because every time the uterus relaxes, the uterine sinuses are opened up and bleeding ensues. As the relaxation of the uterus is produced by the action of epinephrine, the remedy would be to use an adrenolytic drug to eliminate this action.

In searching for a suitable adrenolytic drug, we find that ergotamine has a remarkable pharmacological action for this purpose, in that it is an oxytocic which also has adrenolytic properties, so that it not only contracts the uterus, but at the same time eliminates the adrenergic action and thereby prevents relaxation.

In 1946 we commenced using this drug. As soon as the placenta was delivered, which is in about 3 minutes after the baby is born, 1 c.c. pituitary extract and 1 c.c. ergotamine were given intramuscularly. The oxytocics helped to contract the uterus and the adrenolytic action eliminated the relaxing effect. We used this drug in 1,500 cases and found it accomplished the desired results. However, ergotamine produces a number of untoward reactions, such as nausea, vomiting, and cardiovascular reactions. These we considered were not serious and could be ignored, but four patients developed convulsions, and one patient had a severe bradycardia after receiving the ergotamine. These patients with convulsions had no other condition to which their convulsions could be attributed. They had no proteinuria, no increased blood pressure, and the blood chemistry was normal. They made prompt recovery from their convulsions. Because of these undesirable reactions, however, we reluctantly abandoned the use of ergotamine.

Fortunately, soon after, ergotamine was replaced by a new drug, Dihydroergotamine (D.H.E.) (Sandoz). This drug is used primarily for migraine. It has no oxytocic action, but a greater adrenolytic action than ergotamine. It also has few untoward reactions. As D.H.E. has no oxytocic action, we therefore use 3 drugs: pituitary extract (Pitocin), Dihydroergotamine (D.H.E.), and ergonovine (Ergotrate), after the baby is born and the placenta is delivered.

Technique

The technique is as follows: As soon as the baby is born, a vaginal examination is done and the placenta is promptly delivered, as described by me in 1939.[6] One c.c. (10 units) pituitary extract is given intramuscularly. The uterus is compressed bimanually and held until it is firm. If, after the uterus has contracted, it tends to relax, one ampule (1 mg.) of D.H.E. is given intramuscularly to overcome the relaxing effect of Adrenalin. A cotton sponge is placed in the vagina, and the repair of the episiotomy is now done. The nurse holds the fundus to make certain that it remains contracted. If the uterus persists in relaxing, the D.H.E. is repeated. Twenty minutes after the pituitary extract, one ampule (0.2 mg.) of Ergotrate is given. The uterus will be found firmly contracted and the bleeding under control. If the cervix and uterus still feel flabby, the vagina is packed tightly with plain sterile gauze, which exerts counterpressure against the uterus while the uterus is compressed from above. It is a simple procedure which is very helpful, and is done frequently. The postpartum uterus is never packed, as packing the uterus distends the cavity, opens the sinuses, and causes more bleeding.

We have used Dihydroergotamine (D.H.E.) in 2,000 cases, and find that the uterus remains contracted and bleeding is controlled. Occasionally some untoward reactions from the D.H.E. may occur, but they are of no consequence.

With this conception of the physiology and pharmacology of labor, we can understand why occasionally, in a woman who had strong contractions, a short labor, and an easy delivery, the uterus relaxes and severe bleeding occurs. This cannot be attributed to atony or inertia of the uterus, but is rather caused by the same forces of contraction and relaxation which were acting so powerfully in the first and second stages of labor, and which persist and continue to act in the fourth stage. To overcome this undesirable condition, D.H.E. is given to eliminate the adrenergic action, and thereby stop the relaxations. We find relaxation of the uterus is of more frequent occurrence in the highly emotional type of patient, which condition is very likely also due to the excess epinephrine secretion.

Recently D.H.E. has been used by others in the first stage of labor with the idea of hastening the dilatation of the cervix. This is a dangerous procedure, as the D.H.E. will eliminate the action of the epinephrine, which is essential in producing the relaxing phase, and will thereby throw the uterus into a tonic state. This embarrasses the fetal circulation, and may cause the death of the fetus. Altman and associates[1] (1952) have reported 55 per cent fetal distress with 25 per cent fetal mortality from this use of D.H.E. in the first stage of labor. D.H.E. should be used only in the fourth stage of labor.

Summary

A new interpretation of the physiology of labor is presented.

We know that the posterior pituitary hormone is the active force that causes the contraction of the uterus, but we had no suitable explanation for the relaxation of the uterus in labor.

It is our belief that relaxation of the uterus is produced by endogenous epinephrine, acting reciprocally to the posterior pituitary hormone in the first and second stages of labor, thereby maintaining normal physiological labor.

When the adrenergic force persists and continues to act in the fourth stage of labor, it is harmful, as it causes the uterus to relax, the uterine sinuses thereby to be opened up, and bleeding to occur.

To overcome this adrenergic action, an adrenolytic drug, Dihydroergotamine (D.H.E.) (Sandoz), is used to stop the relaxation of the uterus, and prevent hemorrhage.

We have used the adrenolytic drug in the fourth stage of labor in 3,500 cases, and found it aided in the control of postpartum hemorrhage.

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1831 Grand Concourse

HYPERTENSION FOLLOWING THE USE OF VARIOUS OXYTOCICS*

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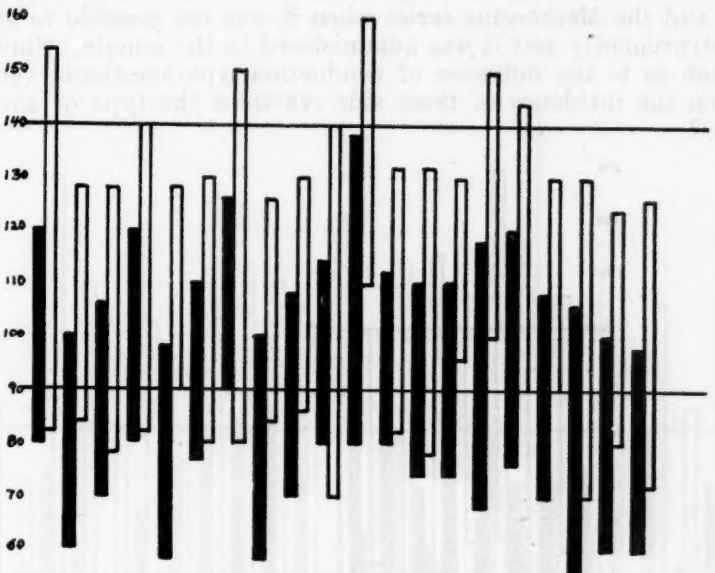
DURING the year from April, 1950, to April, 1951, we noticed a number of patients who complained of nausea, vomiting, severe headache, and developed a sharp rise in blood pressure immediately post partum. Most of these reactions occurred in patients delivered under low spinal anesthesia, but a few were also noted with ether. We became convinced that these symptoms and signs were due to the injection of the oxytocic, since we were unable to find any other cause, and because they occurred within a few minutes following injection of the drug. At that time various routines were used involving the injection intravenously or intramuscularly of ergonovine alone or combined with the intramuscular injection of obstetrical Pituitrin in the management of the third stage of labor.

At first it was thought that contamination by use of a wet-sterilized syringe and needle was the cause, but the reactions continued even when dry-sterilized equipment was used. Assigning the blame to a particular brand of ergonovine was impossible because it occurred with several brands. One manufacturer advocated refrigerated storage but the occasional reactions continued to occur.

A search of the literature pointed up the fact that little has been written about these particular toxic side-effects of the ergotlike preparations, although several authors mentioned them casually. Dieckmann and associates[1] noted nausea and increase in blood pressure following intravenous injection of Pituitrin and of ergonovine in a small series of patients several days post partum. Schade[2] studied the effect of intravenous administration of Methergine and of ergonovine on blood pressure in a large series of cases. He noted that of 200 patients given Methergine, 11 per cent had significant rises in blood pressure; while of 200 patients given ergonovine, 29.5 per cent showed such an increase. Priver and co-workers[3] found that when ergonovine was given intravenously at the beginning and end of the third stage a large percentage of patients complained of nausea, vomiting, and headache, and that these symptoms were concomitant with a rise in blood pressure. They stated that when Methergine was given intravenously in 50 cases all of these systemic manifestations were absent and the greatest elevation of blood pressure was 10 mm. of mercury. Other authors[4, 5] reported no appreciable pressor effects with the use of Methergine. Forman and Sullivan,[6] using Schade's criteria for a significant rise in blood pressure (20 mm. of mercury in either systolic or diastolic reading), found it occurred in 10 per cent of the Methergine cases and in 22 per cent of the ergonovine series.

*Read at the Fourth Annual Meeting of the Interurban Obstetrical and Gynecological Society, Albany, N. Y., Oct. 11, 1952.

Upon resort to textbooks of pharmacology we found that Sollman[7] stated that blood pressure is practically unchanged in man or animal unless the ergot preparation is injected into a vein, when ergonovine tends to raise the pressure slightly. Grollman and Slaughter[8] note that ergotoxine and ergotamine given intravenously cause an abrupt rise in blood pressure obviously due to action on peripheral vessels, and that ergonovine resembles the other members of the ergot group in its actions.



Anes.	Cases	Sig.BP rise pp	Naus/Vom	Head-ache
Spinal	62	14(22.6%)	0	0
Caudal	37	5(13.5%)	0	0
Local	1	1(100%)	0	0
Total	100	20(20%)	0	0

Fig. 1.—No oxytocics.

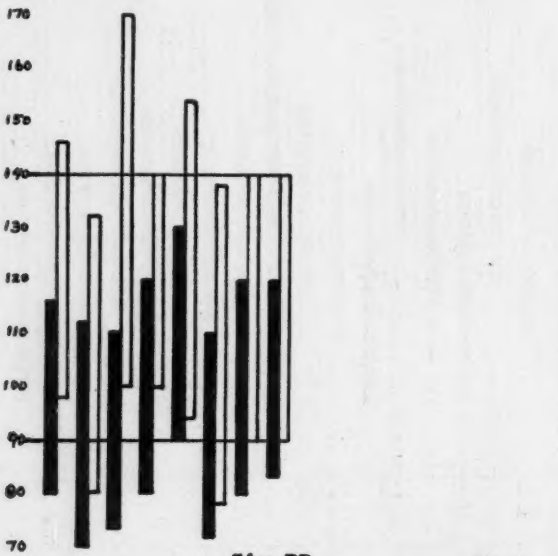
Method and Material

The present study was started in May, 1951, with the avowed purpose of discovering the comparative frequency of occurrence of the side actions mentioned above following the use of ergonovine alone or in combination with Pituitrin, and of Methergine.* The cases were unselected; they were consecutive except when the enthusiasm of the delivery room personnel flagged or when a shortage of help prevented proper observation of the blood pressures. Most of the patients were from the authors' private practice, the balance were private patients of other staff physicians at Lourdes Hospital, except for the patients who were given no oxytocic. These were unselected patients (both ward and private) at the Syracuse Memorial Hospital. The age distribution, parity, and manner of delivery had the usual spread found on any average obstetrical division.

In accordance with the procedure of Schade the admission blood pressure was used as a base line and the pressures were then recorded at intervals of 1, 5, 30, and 60 minutes after injection of the oxytocic, or after delivery of the

*The Methergine used in this study was donated by Sandoz Pharmaceuticals, Division of Sandoz Chemical Works, Inc.

child in the cases where no oxytocic was used. Schade's criteria for a significant rise in blood pressure, as noted above, were used throughout this study. The occurrence of nausea, vomiting, or headache was noted. In the cases where Methergine was used it was given intravenously when the anterior shoulder was born (1 c.c.) and intramuscularly following expulsion of the placenta. The same method was used with ergonovine. Where Pituitrin and ergonovine were used both were given intramuscularly, the former upon birth of the anterior shoulder and the latter after delivery of the placenta. There were a few occasions in the ergonovine and the Methergine series when it was not possible to give the first injection intravenously and it was administered in the muscle. Since there was some question as to the influence of conduction-type anesthesia versus general anesthesia on the incidence of these side reactions the type of anesthesia was also recorded.



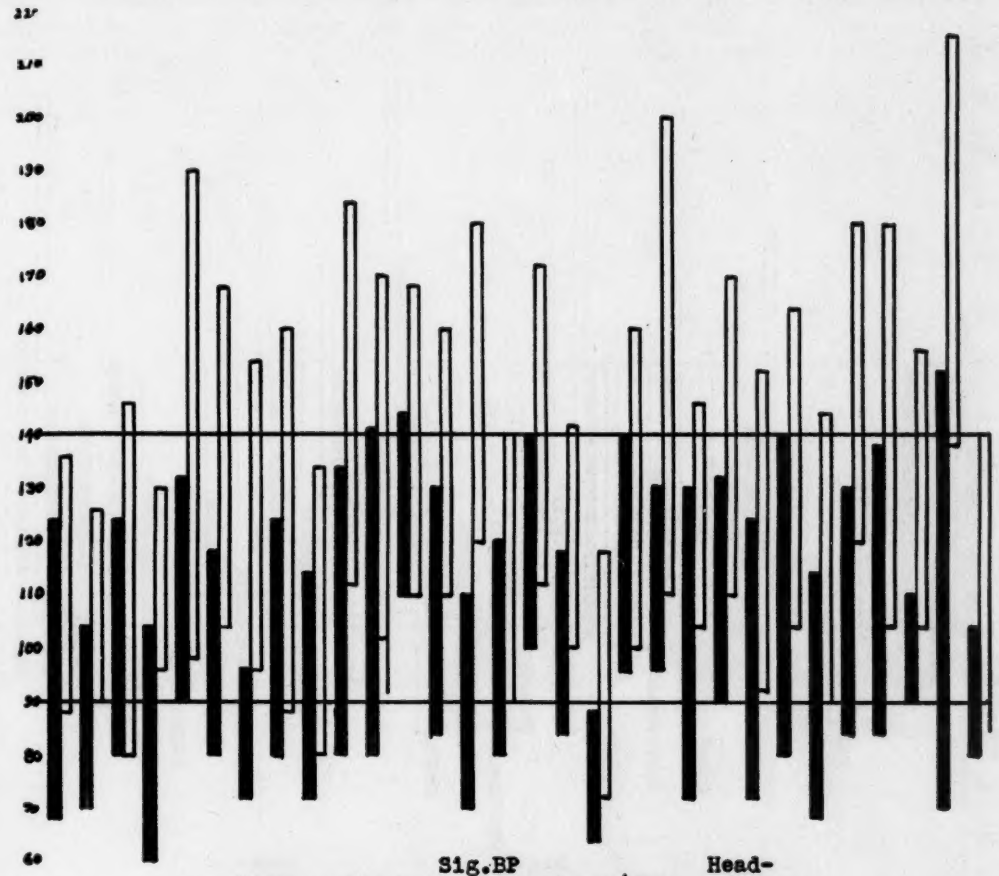
Anes.	Cases	Sig. BP rise pp	Naus/Vom	Head-ache
Spinal	55	5 (9.1%)	6 (10.9%)	0
Ether	38	3 (7.8%)	1 (2.6%)	0
Local	0	0	0	0
Eth/Loc	7	0	0	0
Total	100	8 (8%)	7 (7%)	0

Fig. 2.—Ergonovine.

A total of 682 cases were observed: 100 in which no oxytocic was used, 100 with ergonovine as the sole oxytocic, 216 with Pituitrin and ergonovine, and 266 with Methergine alone. The purpose of collecting and studying a series of patients in whom no oxytocic had been used was to discover the trend of blood pressure for the first hour post partum for comparison with the other series. In the graphic portions of the figures the shaded vertical columns represent the pulse pressures on admission, and the nonshaded columns demonstrate the highest blood pressure attained in the first hour post partum.

In the nonoxytocic group (Fig. 1) we note that there were 20 patients (20 per cent) who showed a so-called significant rise in blood pressure. If we concede that in obstetric practice a systolic reading of 140 or a diastolic of 90 is generally considered the upper limit of normal, then the picture assumes a new light. There were only seven instances (7 per cent) showing a rise to or above these limits.

The ergonovine series (Fig. 2) shows 8 cases (8 per cent) with a significant rise in blood pressure, only 6 (6 per cent) reaching to or above what we generally consider upper normal. One of these was severe, rising to 170/100, without accompanying vomiting or headache. Prior to the beginning of this study with its uniform recording of blood pressures, there were five severe reactions with vomiting and excruciating headache in the preceding 100 patients who were given ergonovine in a similar routine.



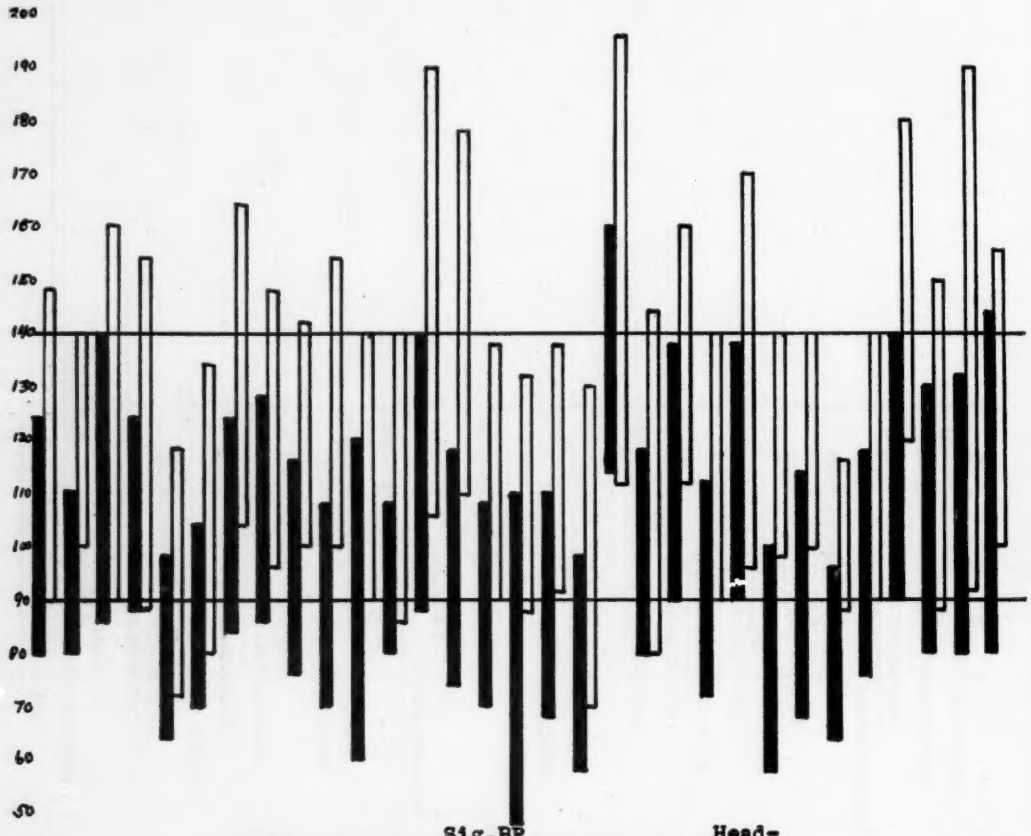
Anes.	Cases	Sig.BP rise pp	Naus/Vom	Head-ache
Spinal	124	17(13.7%)	7(5.6%)	6(4.8%)
Ether	74	8(10.8%)	2(2.7%)	3(4.0%)
Local	10	2(20.0%)	0	0
Eth/Loc	8	3(37.5%)	1(12.5%)	0
Total	216	30(13.9%)	10(4.6%)	9(4.2%)

Fig. 3.—Pituitrin and ergonovine.

In the Pituitrin and ergonovine series (Fig. 3) there were 30 patients (13.9 per cent) who demonstrated a significant rise in pressure, 27 of these (12.5 per cent) reaching or passing 140/90. Of this group 10 (4.6 per cent) developed a severe reaction within the first hour post partum.

Of those patients who received only Methergine (Fig. 4), 31 (11.6 per cent) showed a significant rise in blood pressure, 26 (9.8 per cent) reaching or passing the upper limits of normal. There were 6 (2.3 per cent) who developed severe reactions. All severe reactions in these last two series are graphically illustrated in Fig. 5.

In considering those patients who had an admission blood pressure of 140/90 or more (Table I) we find that of the 75 cases one in the ergonovine series, 5 of the Pituitrin and ergonovine, and 4 of the Methergine group showed a significant rise in pressure for a total of 10 instances (13.3 per cent). There were 7 of these (8.3 per cent) who developed severe reactions, 5 in the Pituitrin-ergonovine group and 2 in the Methergine group. Of the 65 cases in which there was no increase in blood pressure, all but a few demonstrated a moderate fall in pressure, the others remaining fairly stable.



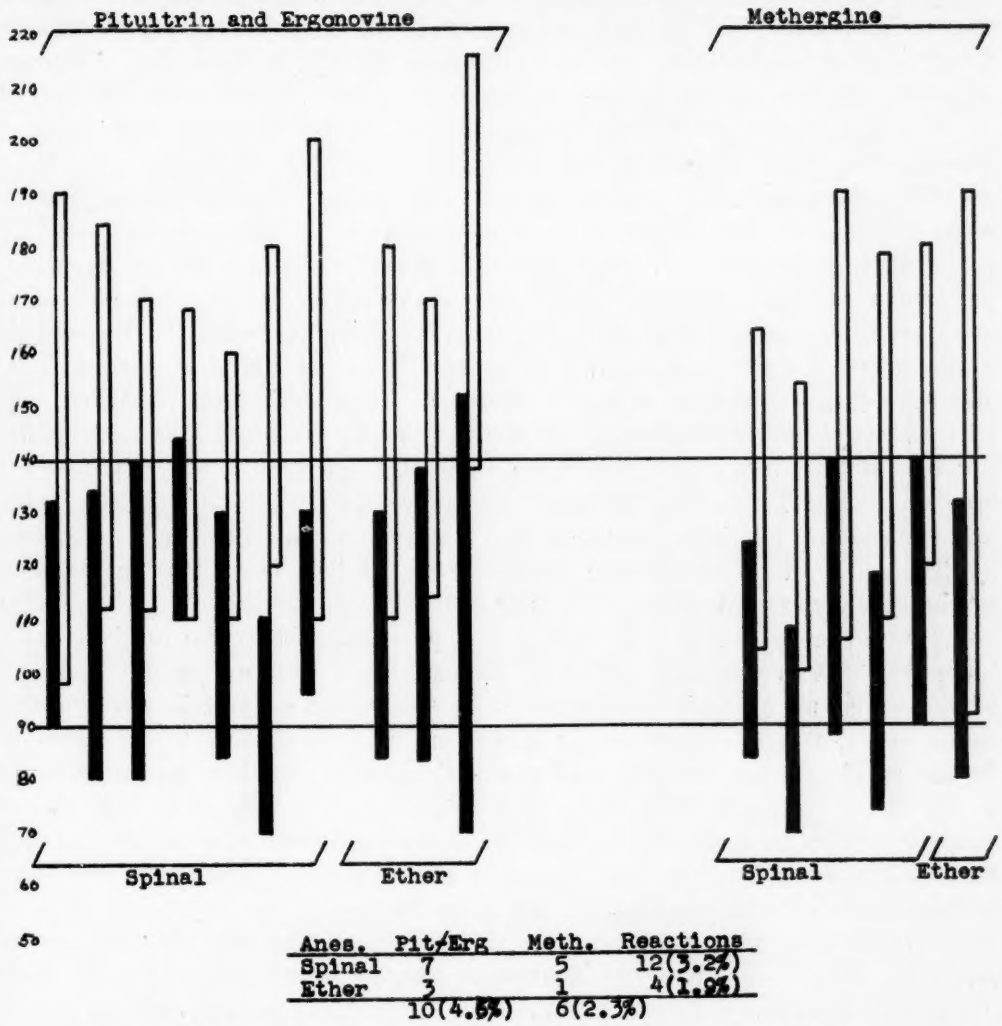
Anes.	Cases	Sig.BP rise pp	Naus/Vom	Head-ache
Spinal	183	26(13.9%)	20(10.9%)	5(2.7%)
Ether	76	3(3.9%)	4(5.3%)	0
Local	1	0	0	0
Eth/Loc	6	2(33.3%)	0	0
Total	266	31(11.6%)	24(9.0%)	5(1.8%)

Fig. 4.—Methergine.

TABLE I. ADMISSION BLOOD PRESSURE 140/90 OR MORE

	CASES	SIGNIFICANT BLOOD PRESSURE RISE POST PARTUM	NAUSEA, VOMITING	HEADACHE	SEVERE REACTION
No oxytocic	4	0	0	0	0
Ergonovine	12	1	1	0	0
Pituitrin, ergonovine	30	5	2	2	5
Methergine	29	4	4	0	2
	75	10 (13.3%)	7 (8.3%)	2 (2.7%)	7 (8.3%)

The relationship of type of anesthesia to changes in blood pressure is shown in Table II, where we find that in 373 patients who were given a conduction-type anesthesia 50 (13.4 per cent) showed a signficant rise in blood pressure when an oxytocic was used. Among 209 patients on whom ether or ether and local were used 20 (9.5 per cent) showed a rise in pressure. Referring back to Fig. 5 we find that 12 cases (3.2 per cent) in the conduction group eventuated



Anes.	Pit/Erg	Meth.	Reactions
Spinal	7	5	12(3.2%)
Ether	3	1	4(1.9%)
	10(4.8%)	6(2.3%)	

Fig. 5.—Severe reactions (nausea, vomiting, sharp blood pressure rise post partum).

TABLE II. RELATION OF ANESTHESIA TO RISE IN BLOOD PRESSURE POST PARTUM

	WITH OXYTOCIC		WITHOUT OXYTOCIC	
ANESTHESIA	NO. OF CASES	SIGNIFICANT BLOOD PRESSURE RISE POST PARTUM	NO. OF CASES	SIGNIFICANT BLOOD PRESSURE RISE POST PARTUM
Conduction	373	50 (13.4%)	100	20 (20 %)
Spinal	362	49 (13.5%)	62	14 (22.6%)
Caudal	0	0	37	5 (13.5%)
Local	11	1 (9.1%)	1	1 (100 %)
General	209	20 (9.5%)		
Ether	188	15 (8.4%)		
Ether and local	21	5 (23.8%)		

in a severe reaction and 4 patients (1.9 per cent) in the general anesthesia series reacted severely.

Summary and Comment

In this study only 6 per cent of the ergonovine series developed a blood pressure rise to or above upper normal limits, in one case rising to 170/100. When we consider that in the preceding 100 ergonovine cases (before blood pressures were recorded at the regular intervals used in this paper) there were 5 instances of marked hypertension with vomiting and excruciating headache, we must conclude that the present series is too small to give a fair picture of the incidence of severe reactions to ergonovine. Suffice it to say that we have become exceedingly cautious in our use of this drug intravenously.

With the larger number of patients included in the Pituitrin and ergonovine series and in the Methergine group the figures are of more significance. In the former group 12.5 per cent developed pressures of 140/90 or more, 4.6 per cent of the cases of the entire series eventuating in severe reactions within one hour following injection of the drugs. This compares with the Methergine group, where 9.8 per cent reached or passed the upper limits of normal, with only 2.3 per cent resulting in severe reactions. Thus Methergine produced only half as many severe reactions. In those patients with an admission blood pressure of 140/90 or more Pituitrin and ergonovine caused 16.6 per cent severe reactions, while Methergine produced 6.9 per cent. Of 186 patients who were normotensive on admission Pituitrin and ergonovine caused severe reactions in 5 (2.7 per cent). Methergine administered to 237 normotensive patients produced severe reactions in 4 (1.7 per cent).

Evaluation of the role of conduction-type anesthesia in the production of these reactions is somewhat difficult. Since 20 per cent of the 100 patients who received no oxytocic and were given conduction anesthesia developed a significant rise in blood pressure, perhaps, in order to be fair to the ultimate degree, we should use that figure in our deliberations. In that case in one-fifth of the 13.4 per cent of 373 patients under conduction anesthesia who developed significant rises in pressure, the rise might be considered due to the type of anesthesia, leaving 10.7 per cent caused by the oxytocics. This figure may then be compared with 9.5 per cent of 209 patients under general anesthesia who developed similar rises in pressure. If one-fifth of the 3.2 per cent severe reactions which occurred under conduction anesthesia are assigned as possibly due to the anesthesia, then only 2.6 per cent of these can be construed as caused by the oxytocics. This compares with 1.9 per cent severe reactions when general anesthesia was used.

It seems obvious that when oxytocics such as these are injected by vein or in the muscle up to 4.6 per cent of the patients may develop marked hypertension, severe headache, and vomiting. These symptoms and signs are less likely to occur when Methergine is used but an incidence of 2.3 per cent with this drug is still too high for one's peace of mind. When these severe reactions do occur, one is faced with the possibility of the rupture of a congenitally weak or a pathologically weakened cerebral blood vessel with all the dangers of such an accident. What can we do (a) to reduce the incidence of these reactions, (b) to reduce the blood pressure when such an alarming reaction does occur?

It is probable that we can reduce the number of reactions principally in four ways: (1) by reduction of dosage; (2) by withholding the drugs in those patients in whom the placenta is promptly expelled with a minimum of bleeding; (3) by oral administration of the drugs, reserving parenteral injection for those patients who develop excessive bleeding; (4) by being especially careful in our use of oxytocics in patients with any degree of toxemia or hypertension.

An interesting observation has been made by one of us (M. A. C.) in that oral administration of 25 mg. of Priscoline (one of the vasodilator drugs) to several patients who had severe reactions reduced the blood pressure to more normal levels and relieved the symptoms within about thirty minutes. The results were not obtained in all of the patients so treated. Certainly further investigation of the various vasodilators in the treatment of the condition would help us.

In summary we believe we have shown that alarming side reactions to these oxytocic drugs do occur in a small but significant number of instances. It is probable that until relatively recently many of us have attributed them to intra- or postpartum toxemia. The absence of albuminuria, edema, nitrogen retention, and the resumption of normal blood pressure levels within a matter of hours should rule out a diagnosis of toxemia. Further study of these drugs from both the clinical and pharmacological aspects is desirable.

Conclusions

1. The oxytocics most commonly used in obstetrics occasionally cause severe hypertension, nausea, vomiting, and excruciating headache.

2. Ergonovine combined with Pituitrin caused these reactions in 4.6 per cent of patients to whom they were given while Methergine caused such reactions in only 2.3 per cent.

3. The lack of severe reactions to ergonovine in this study and our experience of 5 such reactions in 100 patients given this drug prior to the present investigation suggest further study of this drug.

4. We are not prepared to draw a definite conclusion as to the role of conduction-type anesthetics in the causation of these reactions.

The authors wish to express their thanks to the Nursing Staff and House Staff of Our Lady of Lourdes Memorial Hospital, Binghamton, N. Y., and of the Syracuse Memorial Hospital, Syracuse, N. Y. Without their help the collection of the data necessary for this study would have been a much more difficult task.

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THE CONTRACTED UPPER MIDPELVIS

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ATTENTION was recently called[1] to the transversely contracted upper midpelvis as a cause of high occipitoposterior arrests. The purpose of the present communication is to submit data on the clinical significance of bilateral contractions of the upper midpelvis.

The portion of the midpelvis above the ischial spines has heretofore received only cursory attention. There are, however, good reasons to believe that the contracted upper midpelvis is of great clinical significance. This view is based on the following facts, most of which are well known:

1. An arrest of labor may occur at any level of the pelvis between the inlet and the ischial spines.

2. The difficulties in midforceps delivery vary directly with the station of the head in the pelvis—the higher the head, the greater the resistance to rotation and traction.

3. Great resistance to traction is encountered long before the largest diameter of the vertex reaches the level of the ischial spines.

4. The transversely contracted upper midpelvis is an important cause of high occipitoposterior arrests.[1]

5. The extent of possible sagittal expansion sharply diminishes at higher levels of the pelvis. This compensatory factor is, therefore, largely eliminated in the upper midpelvis. The sagittal diameter consequently assumes greater significance at this level of the pelvis.

6. In cases of lower midpelvic contraction, the upper midpelvis is often smaller than the inlet. This important fact, hitherto overlooked, will be demonstrated in the sections to follow.

The Dimensions of the Upper Midplane

The term upper midplane is used in the present study to denote an area in the upper pelvis which extends from the inferior border of the symphysis pubis to the junction of the second and third sacral vertebrae. This plane corresponds closely to an area of the pelvis which is commonly known as "the plane of greatest pelvic dimensions," a designation which is misleading, because it conveys the wrong impression that the diameters of this plane are always the largest in the pelvis.

In 1938,[2] a method was proposed for the internal measurement of the sagittal diameter of the upper midplane, by means of a modified external pelvimeter. The average for this diameter was found to be 12.9 cm. This method lacks the precision of x-ray pelvimetry, but for practical purposes it is sufficiently accurate.

The transverse diameter of the upper midplane cannot be measured directly, because there are no bony points or landmarks from which such measurements can be taken. Recently, however, a method was proposed for obtaining a rough

estimate of this diameter, by taking the mean of the inlet transverse diameter and of the midplane biischial diameter (the diameter between the bases of the ischial spines). The average width of the midplane biischial diameter is 11.15 cm.[3]

The sagittal diameter of the upper midplane, and the midplane biischial diameter were measured by these methods in over 2,000 primiparas. Since 1936, these measurements were supplemented, in selected cases, with x-ray pelvimetry of the inlet by Thoms'[4] method.

The general average for the diameters of the inlet was computed from Thoms'[4] data for the various types of pelves. According to these data, the length of the anteroposterior and transverse diameters of the inlet is 11.6 cm. and 12.5 cm., respectively; and the area of the inlet is 145.0 sq. cm.

The average width of the upper midplane is thus 11.7 cm. (the mean of the inlet transverse and midplane biischial diameters). As already stated, the average length of the sagittal diameter of the upper midplane is 12.9 cm. The average for the area of the upper midplane, in unselected cases, is therefore 150.9 sq. cm., an area which exceeds that of the inlet by approximately 6 sq. cm.

A comparison may now be made of the areas of the inlet and the upper midplane, in contracted pelves. For the present purpose, pelves were classified as contracted if the midplane biischial diameter measured 10.2 cm. or less. Only cases in which major operative intervention was necessary were selected for review. There were 28 such cases in a series of 1,258 primiparas. The results obtained in this study are shown in Tables I and II. It is to be noted that on the average the area of the upper midplane is smaller than the area of the inlet (upper midplane 125.5 sq. cm., inlet 128.6 sq. cm.). In this small series of contracted pelves, the upper pelvis is thus slightly funnel shaped, especially so in the group of midforceps deliveries. The clinical significance of this observation will be pointed out in the sections to follow.

The Contracted Upper Midplane and the Course of Labor

There were 14 cesarean sections with a vertex presentation among the 28 cases of contracted pelvis referred to in Table I. Engagement occurred only in Case 9. A test of labor of 12 hours or over was allowed in Cases 3, 7, and 9, and a test of labor of less than 12 hours in Cases 4, 5, 6, and 8. The remaining sections were elective.

Table II shows the midforceps deliveries in contracted upper midpelves. Slight to moderate resistance to traction was encountered in the low midforceps

TABLE I. CESAREAN SECTION IN CASES OF CONTRACTED UPPER MIDPELVIS

CASE	INLET A.P.	INLET TRANS.	INLET AREA	UPPER MIDPELVIS TRANS.	UPPER MIDPELVIS SAG.	UPPER MIDPELVIS AREA	WEIGHT OF INFANT (GRAMS)
1	9.5	11.0	104.5	10.5	11.0	115.5	2,817
2	10.8	10.1	109.1	10.0	11.2	112.0	3,226
3	11.8	11.5	135.7	10.8	13.0	132.6	4,695
4	9.9	12.0	118.8	11.1	11.0	122.1	3,301
5	9.5	11.8	112.1	10.5	10.8	113.4	2,967
6	10.3	11.6	119.5	10.8	11.0	118.8	3,636
7	11.0	12.0	132.0	11.0	11.0	121.0	4,405
8	10.2	10.7	109.1	10.3	11.3	116.4	3,631
9	11.2	11.2	125.4	10.6	12.0	127.2	3,571
10	10.6	12.2	129.3	11.2	11.5	128.8	3,436
11	11.5	11.5	132.2	10.8	11.8	127.4	3,846
12	10.8	12.6	135.1	11.3	11.5	129.9	3,581
13	11.5	11.2	138.0	11.4	11.8	134.5	3,741
14	10.5	12.6	132.3	11.4	12.0	136.8	3,421
Average			123.8			124.3	3,591

deliveries (Cases 1 to 10 inclusive). Case 11 was a high midforceps delivery, delivered in the occipitoposterior position. Case 12 was a breech presentation, with forceps delivery of the aftercoming head. Cases 13 and 14 are from a series of cases reported in 1936, to which reference will be made later.

It is particularly to be noted that the area of the upper midplane is consistently smaller than the area of the inlet in the above forceps deliveries.

TABLE II. MIDFORCEPS DELIVERY IN CASES OF CONTRACTED UPPER MIDPELVIS

CASE	INLET A.P.	INLET TRANS.	INLET AREA	UPPER MID-PELVIS TRANS.	UPPER MID-PELVIS SAG.	UPPER MID-PELVIS AREA	STA-TION	POSI-TION	RESIST-ANCE TO TRACTION	WEIGHT (GRAMS)
1	11.5	11.7	134.5	10.6	10.5	109.3	3	O.A.	Slight	3,673
2	11.0	12.2	134.2	11.1	11.3	125.4	3	O.A.	Slight	3,012
3	11.2	11.2	125.4	10.5	11.5	120.7	3	O.P.	Moderate	3,616
4	11.8	12.8	151.0	11.5	11.5	132.2	3	O.P.	Moderate	4,385
5	11.1	11.8	131.0	10.5	11.5	120.7	4	O.T.	Moderate	3,846
6	11.0	12.1	133.1	11.0	11.5	126.5	3	O.A.	Moderate	3,421
7	11.2	12.7	142.2	11.8	13.0	153.4	4	O.A.	Slight	3,643
8	12.0	11.5	138.0	10.6	12.8	135.7	3	O.P.	Moderate	3,301
9	13.2	11.0	145.2	10.1	11.5	116.1	3	O.T.	Moderate	3,756
10	11.0	11.2	123.2	10.5	12.0	128.0	3		Moderate	
11	12.3	12.3	151.3	10.8	14.0	151.0	2	O.P.	Great	4,240
12	10.8	11.3	122.0	11.1	11.0	122.1		Breech	Slight	3,256
13	10.2	12.0	122.4	10.6	12.2	119.3	0	O.P.	Great	3,996
14	10.2	11.3	115.3	10.6	10.8	114.5	1	O.P.	Great	3,421
Average			133.5			126.8				3,659

Comments

If a policy of ultraconservatism had been followed in the cases of cesarean section, it is likely that engagement would have occurred after a long test of labor in one or more of the cases in which section was employed while the head was still unengaged. This probably would have resulted in a corresponding increase in the number of difficult high midforceps deliveries. This assumption is supported by the observations made in a series of 1,290 primiparas reported in 1936.[3] In that series of cases there were 16 difficult high midforceps deliveries, 10 of which were done for high occipitoposterior arrest. These untoward results were attributed to a transverse contraction of the lower midpelvis. This explanation still applies to the low midpelvic arrests in that series of cases. However, it now seems that the cause of obstruction in the high midforceps deliveries was due to a complicating contraction of the upper midpelvis, the coexistence of which was then overlooked because no x-ray measurements of the inlet were taken at that time. Since then, an opportunity presented itself for the x-ray measurement of the inlet in two of the difficult high midforceps deliveries and, as expected, a marked degree of contraction of the upper midplane was revealed in both of these cases (Cases 13 and 14, Table II).

The validity of the assumption is also supported by the fact that a marked contraction of the upper midplane was found in the present series of midforceps deliveries, a series of cases which is comparable with the series of 1936.

In view of the foregoing considerations, it is clear that information concerning the capacity of the upper midpelvis may be of great practical value, particularly with reference to a test of labor. A long test of labor may be indicated in cases with even a considerable contraction of the inlet, but not when such a contraction is associated with an equal, or a greater degree of reduction in the area of the upper midplane. It was previously concluded "that high midforceps delivery is contraindicated in pelves in which there is a major

contraction in the narrow pelvic plane.''[3] This conclusion is still applicable, even though the cause of obstruction in high midforceps deliveries must now be placed at the upper midpelvis rather than at the lower midpelvis.

As recently reported,[1] the application of this concept was helpful in the reduction of the incidence of high occipitoposterior arrests, and high midforceps delivery, without an undue increase in the number of cesarean sections.

Summary

1. Attention is called to well-known facts which point to the clinical significance of upper midpelvic contractions.

2. Data are presented which show that in contracted pelves the upper midplane is often smaller than the inlet.

3. Evidence is assembled which indicates that the contracted upper midpelvis is an important factor in the etiology of high occipitoposterior arrests, and is a serious obstacle to high midforceps delivery. In a survey of the pelvis, it is therefore necessary to take into consideration the dimensions of the upper midplane as well as the diameters of the inlet and the lower midpelvis.

4. The conclusion is tentatively drawn that cesarean section may often be indicated, even after engagement of the head, in pelves with a contracted inlet in which the upper midplane is smaller than the inlet.

Addendum.—

The Upper Midplane.—A review of 25 unselected lateral x-ray films showed that the transverse diameter of the upper midplane should be placed at a level approximately two-thirds of the distance from the inlet to the ischial spines. The area of the upper midplane, computed on this basis, would be about 4 sq. cm. smaller than that given in Tables I and II. Thus, the upper midpelvis would be correspondingly even more funnel shaped.

It was also observed that the second parallel plane of Hodge is approximately equidistant between the inlet and the ischial spines. Its transverse diameter may therefore be taken as the mean of the inlet transverse and the midplane biischial diameters. An estimate of the area of this plane may provide valuable supplementary information concerning the capacity of the upper midpelvis.

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AN ANALYSIS OF FIVE HUNDRED FORTY-SEVEN MIDFORCEPS OPERATIONS

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IN RECENT years the trend of many obstetrical services has been to reduce the incidence of midforceps operations by the use of small doses of Pituitrin and in some instances by increasing the incidence of cesarean section. Reid[1] in 1946 reported the incidence of midforceps in ward patients at the Boston Lying-in Hospital to be 0.5 per cent with the treatment of prolonged labor with posterior pituitary extract. Eastman[2] in 1947 reported a reduction in the incidence of midforceps operations from one in every 200 deliveries in the period when Pituitrin was not used to one in every 1,000 deliveries in the period in which Pituitrin was used in carefully selected cases of uterine inertia. Both of these authors have apparently succeeded in reducing midforceps deliveries by augmenting the expulsive powers of the uterus. This has been done in most instances, as our figures later will show, in the presence of an unfavorable mechanism of labor, the main element of which is the position and level of the fetal head.

Many[4, 5, 6] hold the belief that the faulty mechanism can be corrected and that delivery can be accomplished with safety to both mother and fetus by means of the midforceps operation, thus avoiding a prolonged and difficult second stage of labor. The latter is not without hazards to the fetus. This policy has been followed on the obstetrical service at Bellevue Hospital and, in its support, this analysis of the midforceps operations from 1940 to 1951 is presented.

Five hundred forty-seven midforceps operations were performed during this time and there were a total of 21,857 deliveries with an incidence of 2.5 per cent midforceps, or one in 40.

Definition

During the eleven-year period when these operations were performed they were classified as such when the head had reached the level of the ischial spines or lower and was engaged, but had not yet descended to the perineum. Arrest of the fetal head occurred at the following levels: 113 (21 per cent) of the arrests occurred at the level of the spines, 176 (31 per cent) at one finger below the spines, 170 (31 per cent) at two fingers below the spines, 58 (11 per cent) at three fingers below the spines, and in 30 (6 per cent) the arrest occurred with the vertex just above the pelvic floor.

The level of arrest in these cases was based solely on the location of the leading point of the head in relation to the ischial spine, and in all cases the head was engaged. The important relations of the biparietal diameter to the

pelvic planes is not always indicated, as factors such as molding, extension, and asynclitism are not considered. Dennen[3] has presented a classification which more accurately denotes the station of the head in the pelvis. With the information at hand it is not possible to reclassify the cases in this series. It can only be said that none of those forceps operations would be classified by Dennen as high forceps and the majority would be placed in the midforceps group, with the remainder classed as low midforceps. Dennen's classification, which follows, has much to recommend it.

"A high forceps delivery is one in which the biparietal diameter is in the inlet or superior strait of the pelvis and the leading bony point of the head is just above the plane of the ischial spines. Anything higher should be labeled a forceps application to an unengaged head.

"A midforceps delivery is one done on a head, the leading bony part of which is at or just below the plane of the ischial spines with the biparietal diameter below the superior strait. The head nearly fills the hollow of the sacrum.

"A low-midforceps delivery is one in which the biparietal diameter is at or below the plane of the ischial spines with the leading point within a finger breadth of the perineum between contractions. The head completely fills the hollow of the sacrum."

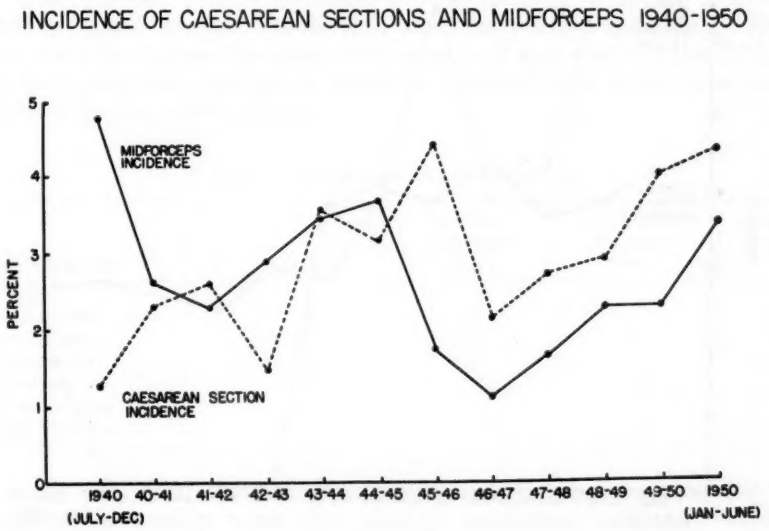

Fig. 1.

Indications

The principal indication for the use of forceps was failure of labor to progress in the second stage for one hour in a multipara and two hours in a primipara. The fetal and maternal results of such deliveries make it difficult to justify further prolongation of the second stage with or without stimulation of uterine contractions, except in most unusual circumstances. Further labor in the second stage may sometimes be indicated in the presence of a dead or abnormal fetus.

Midpelvic arrests were due to uterine inertia, faulty mechanism, lesser degrees of cephalopelvic disproportion, or to a combination of these causes. Fetal distress was a common indication and not infrequently maternal indications for the speedy termination of labor were present, such as toxemia and cardiac disease.

Contrary to the figures which have been quoted, there has been little reduction in the incidence of midforceps operations at Bellevue since 1940. The cesarean section rate has increased slightly and more abruptly since 1948, when a policy of performing sections on all patients with uterine scar was adopted. Other indications for cesarean section have remained about constant. The incidence now stands at slightly greater than 4 per cent. Fig. 1 shows the relationship between the midforceps and cesarean section rates.

Fetal Results

The gross fetal mortality for all deliveries during the period under consideration was 4.42 per cent. When this is corrected for macerated viable stillborn infants, babies with congenital anomalies incompatible with life, and for babies under 3 pounds that died, the fetal mortality was 3.09 per cent. The corrected fetal mortality has shown a slight but steady decline throughout the eleven years.

THE CORRECTED FETAL MORTALITY IN ALL DELIVERIES FROM 1940-1950
COMPARED WITH THE MORTALITY IN MIDFORCEPS DELIVERIES DUE TO TRAUMA

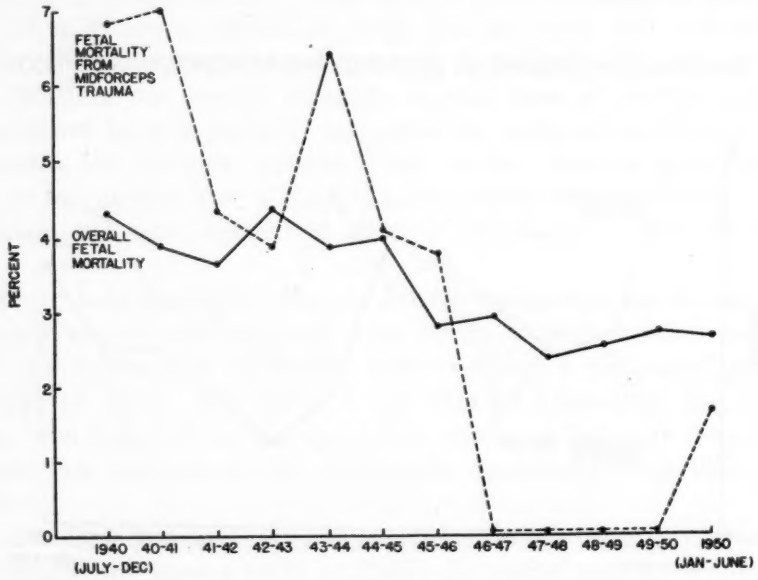

Fig. 2.

In the 547 midforceps deliveries there were 35 fetal deaths, a gross fetal mortality of 6.58 per cent. Corrected for the factors listed above the mortality was 4.75 per cent, or 1.66 per cent higher than the over-all rate. Only 17 of these deaths could possibly be attributed to the trauma of delivery, making a fetal mortality of 3.1 per cent due to this factor. The gross fetal mortality in cesarean sections from 1942 to 1951 as reported by Studdiford and Decker[7] was 8.8 per cent and the corrected fetal mortality 6.2 per cent.

Obviously in those patients delivered by cesarean section factors are frequently present which severely jeopardize the infant. These deaths are rarely the direct result of the abdominal operation. It is apparent from Fig. 2 that there have been only two deaths due to trauma in the last 4½ years of the period analyzed. During this latter interval 329 of the midforceps operations were performed. The fetal mortality as a result of trauma was therefore

0.6 per cent. This is a striking improvement and leads to the belief that midforceps are being utilized less often in unsuitable cases. This operation can and should be a valuable and effective means of delivery, but it requires judgment on the part of the obstetrician. Without judgment it may result in failure and disaster. The decrease in fetal mortality reflects a more careful selection of cases. There are not so many difficult and traumatic high midforceps deliveries being done in recent years. A somewhat greater percentage of cases with the vertex arrested in the upper midpelvis are now terminated by cesarean section. A better choice of anesthesia may be a small factor. There has been a tendency to substitute pudendal block for general anesthesia which has been proved to affect fetal and neonatal mortality.[8, 9]

Not the least important factors in the reduction of fetal mortality and trauma are a better evaluation of the pelvis, a clearer understanding of the mechanics of midpelvic arrests, and the choice of special types of forceps. Their appreciation has led to a forceps delivery closely following the natural mechanism.

Maternal Complications

Table I lists the maternal complications.

The maternal death occurred in an unmanageable psychotic patient who also developed a vesicovaginal fistula and lost her baby. The death occurred in 1940. The patient was a primipara who labored over 24 hours and her mental status made proper evaluation and maintenance therapy impossible. She became febrile during the postpartum period and died on the fifth day. In reviewing her case the conclusion must be reached that today she would have been delivered by cesarean section.

TABLE I. MATERNAL COMPLICATIONS

COMPLICATION	NO.	BARTON FORCEPS (237)	CLASSICAL FORCEPS (83)	KIELLAND FORCEPS (70)
Maternal death	1	1		
Vesicovaginal fistula	2	2		
Cervical lacerations	58	37	10	11
Dührssen's incisions	2	2	1	
Urinary retention	10	6	2	2
Perforation of uterus				1
Laceration of bladder			1	

The maternal death rate in this group is, therefore, about 0.2 per cent. This compares favorably with the over-all maternal mortality rate for this period (0.1 per cent) and the cesarean section mortality rate (0.3 per cent).

The ruptured uterus occurred in a patient delivered by Kielland forceps applied in the classical manner of Kielland. The injury was recognized two and one-half hours after delivery because of the appearance of a suprapubic mass. The patient recovered following a supracervical hysterectomy with a stormy convalescence. Since this case the lower uterine segment has been explored manually in all patients delivered by midforceps. In addition the cervix has been inspected under direct vision.

Fifty-eight cervical lacerations were noted, 37 following the use of Barton forceps (10.6 per cent), 10 following the use of the classical forceps (1.8 per cent), and 11 following the use of Kielland forceps (2.0 per cent). The smaller percentage of lacerations found following the use of classical instruments may be explained on the basis of the simpler mechanism required to deliver the fetus in this position, descent with flexion and only minimal rotation being required. A greater possibility of injury to the anterior vaginal wall, and

sometimes to the bladder, can be expected when the Barton forceps is used, for this type of instrument was more frequently employed for transverse arrests and, by preference, in pelves with platypelloid characteristics. Two vesicovaginal fistulas occurred following the use of Barton forceps.

Fourteen per cent of the patients were morbid on the 100° F. standard during the puerperium. Ten per cent were morbid on the 100.4° F. standard and 7.6 per cent on the 101° F. standard. The morbidity since the advent of sulfonamides and more especially since the introduction of penicillin has shown a steady decline, and is much lower now than this eleven-year average would indicate. During the last 12 months of the series these figures are 7.3 per cent, 6.1 per cent, and 4.3 per cent, respectively.

Management of Midpelvic Arrests

One of the most illuminating factors in the understanding of midpelvic arrests has been derived from the utilization of x-ray pelvimetry in as many cases as possible. As an established policy, x-ray pelvimetry has been carried out prior to delivery on patients who attend the prenatal clinic and are found to give clinical evidence of abnormalities of the bony pelvis. Similar studies are carried out as often as possible, sometimes during labor and sometimes during the postpartum period, in patients delivered by midforceps, regardless of the clinical classification of the pelvis. It is to be remembered that about 40 per cent of these patients are admitted in labor with no antepartum observation. The x-rays are interpreted and classified according to the method of Caldwell and Moloy by members of the obstetrical staff actively engaged in the care of the patient. An accurate record is then made of the features of the pelvis, the details of labor, and the method of delivery. There is little value in having such x-rays interpreted by individuals totally unaware of the mechanism of labor. The implications of the latter remark are obvious. Antepartum films are kept on file on the delivery room floor and are immediately accessible at all times.

Films which could be satisfactorily classified were obtained on 316 (58 per cent) of the patients here reported.

There were 69 anterior arrests and satisfactory x-rays were obtained in 39 (55 per cent) of these. The position of the arrested head and the type of pelvis are shown in Table II.

Most of these arrests occurred in a gynecoid type pelvis. The one unusual exception is the arrest which occurred in the gynecoid pelvis with platypelloid

TABLE II. ANTERIOR ARRESTS

TYPE OF PELVIS	POSITION OF ARREST				
	LEFT OCCIPITO-ANTERIOR	RIGHT OCCIPITO-ANTERIOR	DIRECT OCCIPITO-ANTERIOR	RIGHT BROW ANTERIOR	RIGHT MENTUM ANTERIOR
Gynecoid pure	16	5	3	1	
With android tendencies	3	1			
With platypelloid tendencies	1				
With anthropoid tendencies	1	1	1		
Android	2				
With gynecoid tendencies	1				
Anthropoid	1				
With platypelloid tendencies	2				
Clinically ample	12	9			1
Not estimated	5	2	1		
Total	44	18	5	1	1

tendencies. Delivery in this instance might have been accomplished more easily by rotating the vertex to the transverse position before bringing the head through the midpelvis. Fifty-five of the patients were delivered with Haig-Ferguson forceps, five with Dewees forceps, two with Bailey-Williamson forceps, two with Elliott forceps, one with Tucker-McLean forceps, and three with Kielland forceps. Personal preference undoubtedly played some part in the choice of instruments. However, it is very evident that the Haig-Ferguson forceps is the favored classical-type instrument at Bellevue Hospital. The forceps has a good cephalic curve and a simple but effective axis traction bar. The axis traction principle is important and in all but six of these deliveries instruments incorporating this feature were used.

A word of explanation is necessary regarding the three cases of anterior arrest delivered with Kielland forceps. In the first case the position was right brow anterior and attempts to flex the head with Kielland's and then with classical forceps were unsuccessful. The Kielland forceps were then used to extend the vertex, converting the brow to a face presentation, and then to rotate the face anteriorly and deliver the baby in the anterior mentum position. This maneuver is helpful provided no element of disproportion exists. Such faulty mechanisms cannot always be corrected, in which event cesarean section becomes preferable to forceps delivery in the interest of the fetus. In both the other cases the Kielland forceps were used because of the operator's preference.

Three hundred two arrests occurred in the transverse position. Of these, 184 (61 per cent) patients had satisfactory x-ray pelvimetry. Table III shows the correlation of the position of the arrested head and type of pelvis and also the method selected for delivery in each instance.

TABLE III. TRANSVERSE ARRESTS

	POSITION OF ARREST				METHOD OF DELIVERY			
TYPE OF PELVIS	LEFT OCCIPITO-TRANSVERSE	RIGHT OCCIPITO-TRANSVERSE	RIGHT BROW TRANSVERSE	RIGHT MENTUM TRANSVERSE	BARTON FORCEPS	KIELLAND FORCEPS	MANUAL ROTATION AND CLASSICAL FORCEPS	CLASSICAL FORCEPS IN TRANSVERSE
Gynecoid								
Pure	42	38	1		69	9	3	
Android tendencies	6	9			12	3		
Flat tendencies	5	7			10	1	1	1
Anthropoid tendencies	2	3			4			
Android								
Pure	7	1			6		1	1
Gynecoid tendencies	9	5			12	1	1	
Flat tendencies	9	6			12	1	1	1
Platypelloid								
Pure	12	7			18		1	
Gynecoid tendencies	3	4			6	1		
Android tendencies	2							
Anthropoid								
Pure	3	1			3		1	
Gynecoid tendencies		2			1	1		
Clinically ample	40	53	1					
Not estimated	10	13		1				
Total	150	149	2	1				

In three of the cases of transverse arrest which occurred in the anthropoid type of pelvis delivery was by means of the Barton forceps. This was a poor selection, as the best diameters of the pelvis were not utilized. The vertex in each instance should have been brought through the midpelvis in the anteroposterior or in the oblique diameter. However, no serious difficulties were encountered in any of these cases, live, uninjured infants being obtained.

Most of the transverse arrests occurred in gynecoid pelves, although the incidence of the platypelloid and android pelves in such cases is striking.

A knowledge of pelvic architecture is of primary importance in an analysis of the arrest and in an intelligent management of the problem. By utilizing the best available diameters, maternal and fetal injury can be avoided, and in some instances only by utilizing these diameters can vaginal delivery be accomplished. The method of delivery in all transverse arrests is summarized in Table IV.

TABLE IV. METHOD OF DELIVERY OF TRANSVERSE ARRESTS

Barton forceps (including right brow transverse and right mentum transverse)	250	82.7%
Kielland forceps	25	8.2%
Manual rotation to an anterior position and classical forceps	21	6.9%
Classical forceps applied in the transverse position	6	1.9%

The Barton forceps are ideally suited for transverse arrest in the flat pelvis or in pelves with ample transverse measurements.[10, 11] The forceps is easily applied and can readily correct asynclitism in most instances. The design of the forceps and the use of the axis traction principal permit the utilization of the roomier posterior segment of the pelvis. Kielland forceps are not as well suited for these arrests as the straight shank and lack of pelvic curve direct the line of traction against the symphysis and away from the hollow of the sacrum. The Kielland forceps is well suited for rotation but this is not desirable in cases where the transverse diameter is the best available. Some transverse arrests can be converted to an anterior position by manual rotation before applying classical blades. This is satisfactory if there is available room in the anteroposterior diameter. In many instances the vertex will slip back to the original position before the classical instrument can be applied. We do not favor application of classical forceps to the head in the transverse position as an accurate application is almost impossible to obtain. With a pelvic application of these instruments, serious injury may result to both the mother and the fetus.

One hundred seventy-six arrests occurred with the occiput in the posterior position and of these 93 had satisfactory x-ray pelvimetry. The position of the arrested head and type of pelvis are shown in Table V.

The predominance of the gynecoid pelvis is again apparent. The anthropoid pelvis and those with anthropoid tendencies accounted for the majority of the remainder.

The method of delivery in posterior arrests is shown in Table VI.

Four of the arrests which occurred in anthropoid pelves were manually rotated to the transverse position and delivered through the pelvis in that diameter. The most adequate diameter was not utilized in these cases as more room was available in the anteroposterior. Again it can be noted that serious difficulty in these deliveries was not encountered and living, uninjured babies were obtained.

The preference for the Barton forceps is reflected in these figures. In most instances the delivery was accomplished without undue difficulty, especially in the flat pelves or in pelves with flat tendencies. In only 10 instances

was the vertex delivered in the posterior position. Delivery face-to-pubes is not advocated as a routine procedure, but may occasionally be indicated when rotation proves to be difficult. Some of these deliveries occurred because of failure to diagnose the position properly. There was one fetal death as a result of intracranial trauma in a baby delivered face-to-pubes, and inability to rotate the head might have served as a warning of impending difficulty.

TABLE V. POSTERIOR ARRESTS

TYPE OF PELVIS	POSITION OF ARREST			
	LEFT OCCIPITO-POSTERIOR	RIGHT OCCIPITO-POSTERIOR	DIRECT OCCIPITO-POSTERIOR	RIGHT MENTUM POSTERIOR
Gynecoid				
Pure	15	28	4	1
Android tendencies	1	4		
Flat tendencies		1		
Anthropoid tendencies	2	5		
Android				
Pure		1	2	
Gynecoid tendencies		3	1	
Flat tendencies		2		
Anthropoid tendencies	1	1		
Platypelloid				
Pure		3	1	
Gynecoid tendencies		1		
Anthropoid				
Pure	8	5	3	
Clinically ample	13	42	14	
Not estimated	8	5	1	
Total	48	101	26	1

TABLE VI. METHOD OF DELIVERY OF POSTERIOR ARRESTS

TYPE OF PELVIS	MANUAL ROTATION TO TRANSVERSE AND BARTON FORCEPS	MANUAL ROTATION ANTERIOR AND CLASSICAL FORCEPS	KIELLAND FORCEPS	CLASSICAL FACE-TO-PUBES	KIELLAND FACE-TO-PUBES
Gynecoid					
Pure	18	3	23	3	1
Android tendencies	2	1	1	1	
Flat tendencies	1				
Anthropoid tendencies	1		6		
Android					
Pure	1			1	
Gynecoid tendencies	3		1		
Flat tendencies	1		1		
Anthropoid tendencies	2				
Platypelloid					
Pure	4	1			
Gynecoid tendencies	1				
Anthropoid					
Pure	4		8	2	
Not classified	41	7	41	2	1
Total*	79 (42.6%)	12 (6.8%)	81 (44.8%)	9 (5.1%)	2 (1.1%)

*Three Scanzoni maneuvers not listed.

Experience in this series shows the Barton forceps to be an instrument particularly suited for transverse positions or posterior positions which can be rotated to the transverse diameter of the pelvis; especially where posterior

asynclitism (posterior parietal presentation) exists. In the latter instance application of Kielland forceps may be impossible.[12, 13]

The selection of forceps is of utmost importance. We do not believe that all midpelvic arrests can be treated with a single instrument. From what has been said, the often-quoted advice to learn to use one type of instrument well and to forget the rest, is utter nonsense. Instruments are available specially designed to provide the most effective axis traction with the head in the transverse diameter (Barton forceps); particularly designed for rotation (Kielland); and for delivery of the head in the anteroposterior diameter (the classical forceps). Provided the operator is aware of the varying factors involved in midpelvic arrests and possesses a knowledge of the mechanics of descent and rotation of the fetal head, delivery can be accomplished with very little risk to the mother and fetus, provided suitable instruments are selected.

Failed Forceps

It is inevitable that in any large series of midforceps deliveries occasionally attempts will be met with failure. This undoubtedly represents poor judgment in some aspect of the evaluation of the delivery. In addition to the cases presented in the foregoing, there were nine unsuccessful attempts at delivery after forceps had been applied. In five of these cases efforts were being made to overcome cephalopelvic disproportion of too great a degree. Three of these cases were terminated eventually by cesarean section and living babies were obtained. In the other two, delivery was accomplished by version and breech extraction; one baby was stillborn and the other died in the immediate neonatal period, both as a result of trauma. In one case forceps was applied to the second twin and removed when the head was found unengaged. This baby was delivered by version and breech extraction; the mother, incidentally, died of a postpartum hemorrhage. Another attempted delivery with Barton, Kielland, and Haig-Ferguson forceps failed because of the presence of an unsuspected contraction ring. The other two failures occurred in patients with brow presentations where efforts to flex and extend the head were unsuccessful. The last three babies were delivered by cesarean section.

Four of these nine babies were stillborn or died soon after birth as a result of trauma inflicted during attempts to deliver them by forceps. The failure to deliver the fetus can be rectified only if the operator realizes that some factor has been miscalculated and his efforts to deliver are not carried to extremes. Vigorous traction should be avoided and in the event that delivery is not readily accomplished, the forceps should be removed and delivery completed by cesarean section. When forceps fail there is little reason to believe that a live, uninjured baby can be obtained by version and breech extraction.

One of the most frequent errors is in the estimation of the size of the baby. In four instances, the babies weighed more than 8½ pounds and the pelves were inadequate for such large infants.

The pelvis with converging side walls and lateral bore, but with a good inlet which allows rapid descent to the midpelvis, can lead the obstetrician to a false sense of confidence. With further descent diameters diminish and delivery may even be impossible. Bunim[14] has aptly described this as the "obstetrical trap." Unless efforts to deliver are discontinued in time, irreversible damage to the infant may be the result.

Summary and Conclusions

1. An analysis of 547 midforceps deliveries is presented with a gross fetal mortality of 6.58 per cent and a corrected fetal mortality of 4.75 per cent

2. Factors responsible for the lowering of the fetal mortality rates in infants delivered by midforceps are presented.

3. The importance of selecting the proper forceps for each delivery is stressed.

4. Emphasis is placed on the evaluation of the bony pelvic architecture in determining the means by which delivery shall be accomplished.

5. We believe that midforceps is a valuable method of delivery and can be a safe method when all factors are considered and more difficult and hazardous cases are eliminated.

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"COMBINED" AND FREE PLASMA ALPHA-AMINO NITROGEN IN NORMAL PREGNANCY AND TOXEMIA

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SINCE Hoffström's[1] early study, a considerable body of literature has appeared concerning over-all nitrogen metabolism, or balance, in gestation. These data leave little doubt that during the normal pregnant state on adequate intakes of protein there is a tendency for the maternal organism to store nitrogen (Macy and Hunscher,[2] and a number of authors have emphasized the desirability of abundant dietary protein as insurance against the development of various complications of pregnancy including toxemia.[3, 4, 5, 6, etc.] The available literature is poor, however, in reports relating to the intermediary metabolism of nitrogen in pregnancy. As a point of departure for studies of this nature now in progress, the preliminary observations on conjugated and free plasma amino nitrogen included in this report were made.

Material and Methods

Total free α-amino nitrogen was determined in plasma of normal and toxemic white patients at intervals during gestation and the early puerperium. Postabsorptive venous blood specimens were obtained with minimal stasis with heparin at a concentration of 0.2 mg. per milliliter of blood as the anticoagulant. Immediately following collection of blood specimens, the plasma was separated by centrifugation and picric acid filtrates were prepared. Determinations of α-amino nitrogen were made at least in duplicate by the ninhydrin-manometric method of Hamilton and Van Slyke[7] with the addition of hydrazine sulfate to the lactic acid reagent.[8] Duplicate analytical values corresponded within ± 1 per cent.

Blood urea nitrogen was determined in tungstic acid filtrates of oxalated blood by a steam distillation method employing a modification of Redemann's[9] apparatus. Amino nitrogen values were then corrected for urea hydrolysis.[7] Plasma specific gravity was determined by the technique of Phillips and associates.[10]

Estimations of "combined" α-amino nitrogen were made on additional normal pregnant, healthy nonpregnant women, and patients with toxemia of pregnancy. Plasma dialysates were prepared by the method of Hamilton and Archibald[11] with du Pont PT 600 Cellophane as the dialyzing membrane.*

*The author is indebted to Mr. C. L. Blair of the Film Department, E. I. du Pont de Nemours & Company, for his cooperation in furnishing this material.

Dialysis was performed at 5 ± 1° C. for 5 hours. Aliquot portions of plasma were used for reference analyses on picric acid filtrates. Following concentration of dialysate and analysis of aliquot portions for α-amino nitrogen, hydrolysis was carried out in 4N hydrochloric acid for 24 hours in sealed tubes placed in a flask of boiling water fitted with a reflux condenser. The dialysate was reduced to dryness in vacuo, distilled water added, and again taken to dryness to remove the hydrochloric acid. After the addition of water, aliquots were analyzed for α-amino nitrogen after adjustment to pH 2.5 by solid citrate buffer. "Combined" α-amino nitrogen was calculated by difference in values obtained before and following hydrolysis.

Results

In Fig. 1 are plotted free plasma α-amino nitrogen values determined at intervals during pregnancy and the early puerperium for eight patients in good nutritional status whose prenatal course was normal. Two patients (Ws, Ht) were delivered by cesarean section because of cephalopelvic disproportion after a trial of labor. The mean (4.11) and ± 2 σ (1.54) for normal nonpregnant women are superimposed for comparison. It is apparent that although the antepartum α-amino nitrogen values are for the most part within two standard deviations of the normal mean, the tendency to low values is definite. Between 24 and 72 hours following delivery, an increase occurs, with a tendency to approximate mean normal levels. It is of interest that this tendency is seen in the data for both patients delivered by cesarean section.

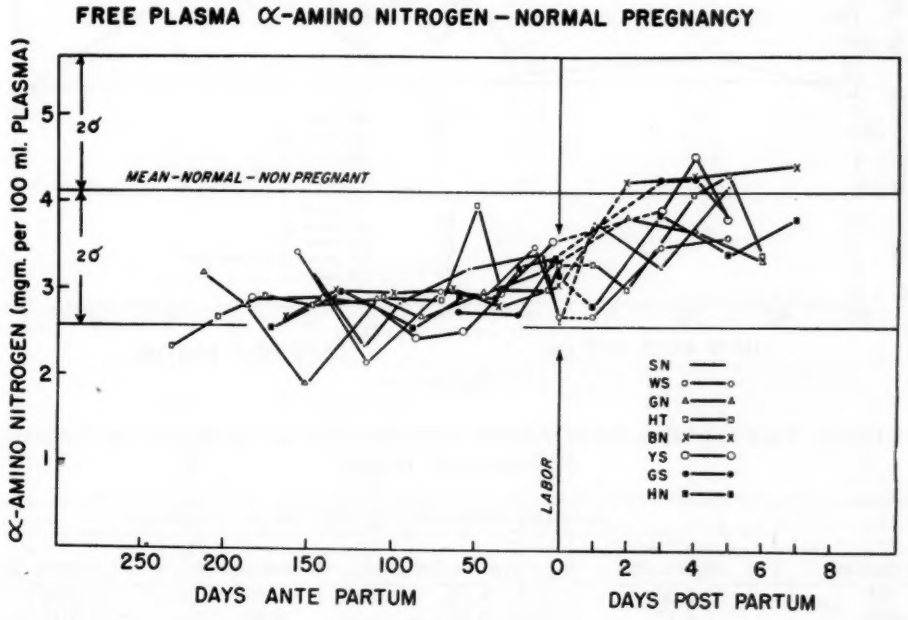

Fig. 1.

The plasma α-amino nitrogen concentration of pre-eclamptic patients is similarly plotted in Fig. 2. Mean normal and ± 2 σ values are shown. The number of antepartum determinations for this group of patients was limited by the time of onset of toxemia. One subject (Kr) was initially included in the normal series, but subsequently developed pre-eclampsia. It is apparent

from reference to Fig. 2 that plasma α-amino nitrogen in the pre-eclamptic patient is somewhat variable, but that the values obtained were within normal limits included by ± 2 σ. A postpartum increase, as found for normal subjects, is also shown.

Of incidental interest was the tendency to low blood urea nitrogen values for all patients studied. The concentration of plasma protein was found to be slightly lower for pre-eclamptic patients than in uncomplicated pregnancy.

In Tables I through V the estimations of "combined" or conjugated α-amino nitrogen are tabulated for normal nonpregnant women, antepartum and postpartum normal and pre-eclamptic patients. Attention is directed to the close correspondence between α-amino nitrogen values determined on picric acid filtrates and plasma dialysates. The range, mean, and standard deviation for the various groups investigated are shown in Table VI. By calculation of "t values"[12] no significant difference was found between the mean values shown.

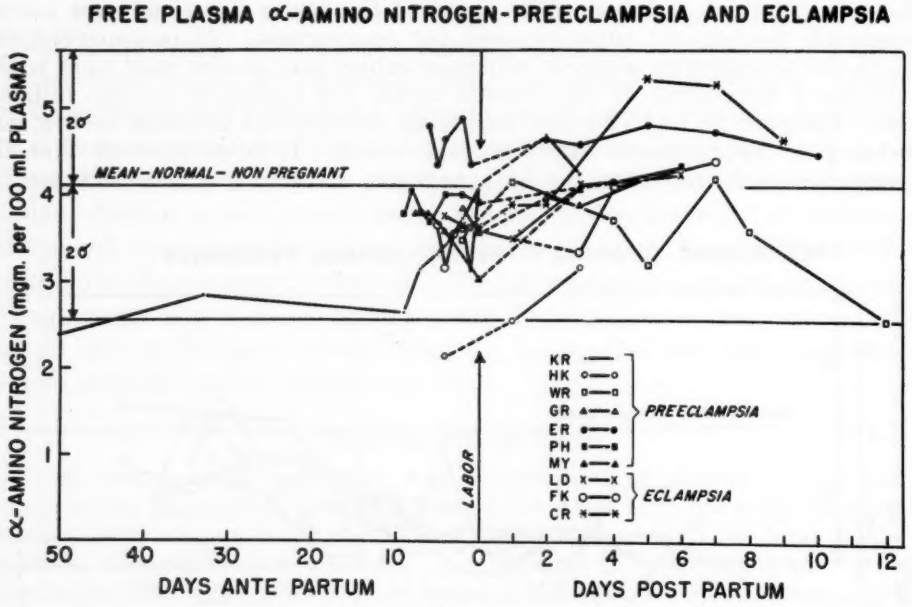

Fig. 2.

TABLE I. FREE AND "COMBINED" α-AMINO NITROGEN VALUES FOR PLASMA OF NORMAL NONPREGNANT WOMEN

SUBJECT	α-AMINO NITROGEN (MG. PER 100 ML. PLASMA)			
	PICRIC ACID FILTRATE	DIALYSATE	HYDROLYSATE	"COMBINED"
Al	5.20	5.15	6.05	0.90
Cl	5.17	5.20	6.32	1.12
Br	5.00	5.04	5.55	0.51
Hi	3.75	3.71	4.39	0.68
Do	3.99	4.03	4.42	0.39
Ed	4.12	4.14	4.83	0.69
Ba	4.58	4.64	4.86	0.22
Ho	3.49	3.55	4.52	0.97
Mc	4.75	4.82	5.23	0.41
Fe	3.78	3.76	4.19	0.43

TABLE II. FREE AND "COMBINED" α-AMINO NITROGEN VALUES FOR PLASMA OF NORMAL ANTEPARTUM PATIENTS

SUBJECT	WEEKS OF GESTATION	α-AMINO NITROGEN (MG. PER 100 ML. PLASMA)			
		PICRIC ACID FILTRATE	DIALYSATE	POST HYDROLYSIS	"COMBINED"
Cr	29	3.17	3.13	3.80	0.67
Ky	36	4.05	4.07	4.68	0.61
Ys	31	2.47	2.44	3.18	0.74
Ml	32	3.28	3.36	3.95	0.59
Lk	32	3.14	3.14	3.56	0.42
Cx	39	3.69	3.69	3.99	0.30
Gh	36	3.85	3.82	4.36	0.54
Cn	30	3.94	3.90	4.39	0.49
Jr	40	4.25	4.30	4.51	0.21
Vs	37	4.23	4.22	4.87	0.65

TABLE III. FREE AND "COMBINED" α-AMINO NITROGEN VALUES FOR PLASMA OF NORMAL POSTPARTUM PATIENTS

SUBJECT	DAYS POST PARTUM	α AMINO NITROGEN (MG. PER 100 ML. PLASMA)			
		PICRIC ACID FILTRATE	DIALYSATE	POST HYDROLYSIS	"COMBINED"
Lh	3	3.45	3.40	4.18	0.78
Ch	4	3.56	3.55	4.01	0.46
Ky	3	3.29	3.31	3.72	0.41
Sk	4	2.99	3.03	3.46	0.43
Ml	3	2.72	2.70	3.12	0.42
Me	3	4.38	4.36	4.79	0.43
Hs	2	3.99	3.98	4.09	0.11
Ys	4	4.55	4.53	5.21	0.68
Ol	3	4.23	4.26	4.78	0.52
My	3	3.89	3.91	4.25	0.34

TABLE IV. FREE AND "COMBINED" α-AMINO NITROGEN FOR PLASMA OF PRE-ECLAMPTIC PATIENTS ANTE PARTUM

SUBJECT	WEEKS OF GESTATION	α-AMINO NITROGEN (MG. PER 100 ML. PLASMA)			
		PICRIC ACID FILTRATE	DIALYSATE	POST HYDROLYSIS	"COMBINED"
Ph	28	3.78	3.80	4.28	0.48
Ph	29	4.00	3.98	4.29	0.31
Ps	30	3.36	3.33	3.62	0.29
My	38	3.78	3.74	4.13	0.39
Te	40	3.15	3.13	4.11	0.98
Ae	38	3.98	4.03	4.84	0.81
Cs	42	3.49	3.45	4.03	0.58
Co	40	4.94	4.94	5.40	0.46
Hs	35	3.24	3.20	3.69	0.49
Or	32	3.15	3.18	3.66	0.48
Hd	36	3.96	3.91	4.36	0.45
Hd	37	4.06	4.02	4.83	0.81

TABLE V. FREE AND "COMBINED" α-AMINO NITROGEN FOR PLASMA OF PRE-ECLAMPTIC PATIENTS POST PARTUM

SUBJECT	DAYS POST PARTUM	α-AMINO NITROGEN (MG. PER 100 ML. PLASMA)			
		PICRIC ACID FILTRATE	DIALYSATE	POST HYDROLYSIS	"COMBINED"
Je	3	3.97	4.00	4.59	0.59
Ph	6	4.33	4.36	5.02	0.66
My	3	4.09	4.06	4.57	0.51
Hh	3	3.88	3.85	4.01	0.16
Fg	1	4.52	4.46	4.88	0.42
Cs	3	3.99	4.01	4.63	0.62
Bn	3	3.87	3.92	4.60	0.58
Hd	3	4.56	4.51	5.06	0.55
Bs	3	4.40	4.35	5.12	0.77
Hl	3	4.96	4.90	5.30	0.40

TABLE VI. RANGE, MEAN, AND STANDARD DEVIATION FOR "COMBINED" α-AMINO NITROGEN VALUES

CLASSIFICATION	MG. FOR 100 ML. PLASMA		
	RANGE	MEAN	S. D.
Normal: nonpregnant	0.22 - 1.12	0.63	0.28
Normal: ante partum	0.21 - 0.74	0.52	0.16
Normal: post partum	0.11 - 0.78	0.46	0.17
Pre-eclampsia: ante partum	0.29 - 0.98	0.55	0.20
Pre-eclampsia: post partum	0.16 - 0.77	0.54	0.17

Comment

The observations on free α-amino acid nitrogen in plasma during normal pregnancy and the puerperium confirm and extend the results reported by Bonsnes.[13] The specificity of the reaction between triketohydrindenehydrate (ninhydrin) and free amino acids has been pointed out by Van Slyke and his co-workers, and Bonsnes[13] has discussed the diverse observations on amino nitrogen in pregnancy reported by earlier authors using techniques based on other analytical principles. The ninhydrin-manometric method remains the most satisfactory technique available for the quantitative determination of α-amino acid nitrogen, and, within the limits of error inherent in this method, the analytical values included in this report are considered valid. In this connection, it is of interest to note that the mean value of 4.11 mg. per cent obtained for 14 normal nonpregnant women (standard deviation 0.77) corresponds closely to the normal mean of 4.07 (standard deviation 0.76) reported by Hamilton and Van Slyke.[7] There is similar correspondence to Bonsnes'[13] value of 4.2 mg. per cent although his data are uncorrected for urea hydrolysis.

No satisfactory explanation can be offered at the present time for the decrease in free α-amino nitrogen concentration of plasma in pregnancy, nor for the trend toward normal levels in the early puerperium, variations that are present in the data of other authors.[13] Conceivably, such changes could be simply based on failure to compensate for the normal gestational increase in plasma volume[14] or to increased renal losses of amino acids.[15] The additional possibility exists, however, that these changes are subtle reflections of the known alteration in nitrogen metabolism,[2] or representative of obscure changes in the "metabolic pool" of nitrogen,[16] in response to pregnancy. As the

patients selected for the normal series were clinically well nourished, it seems unlikely that malnutrition was a factor in producing the prenatal lowering of α-amino nitrogen levels as described by Man and associates[17] for certain classes of surgical patients.

The values for plasma α-amino nitrogen in toxemia show no apparent deviation from the normal changes in pregnancy, although greater individual variation in consecutive determinations seems to occur. The bulk of these data was obtained within a few days of delivery and in the early puerperium, however. Selection of patients for this series was based on admission blood pressure determinations in excess of 140/90, with the presence of albumin in a urine specimen obtained by catheterization. As only total α-amino nitrogen concentration was measured, these data do not necessarily exclude the possibility of significant alterations in individual amino acid levels or metabolism in the toxemias of pregnancy.

The difficulties encountered in the determination of conjugated or "combined" α-amino nitrogen have been pointed out by Christensen[18, 19] who has outlined the analytical criteria for estimation of these compounds in blood and plasma. The usage of the term "combined" α-amino nitrogen is preferred to peptide nitrogen for the reasons noted by this investigator.[18]

The close correspondence between the values for α-amino nitrogen obtained on picric acid filtrates of plasma and on plasma dialysates (Tables I through V) is interpreted as evidence, but not absolute proof, that proteolysis did not occur during the period of dialysis under the conditions adhered to in these analyses. The values for "combined" amino nitrogen are within the normal range for plasma previously reported by Christensen[18] although the mean value given by this author is 0.9 mg. per cent (standard deviation 0.44).

In the postabsorptive state no significant variation was found between the data for normal and toxic pregnancy, nor between these categories and values in the nonpregnant (Table VI). This finding is in sharp contrast to the changes in free α-amino nitrogen observed. This finding is difficult to interpret, particularly so in view of the debated metabolic function of plasma peptides in the postabsorptive state.[18] As noted, the observations included in this report are of a preliminary nature, and further interpretation must await the result of studies now in progress designed to investigate the metabolic role of the various nitrogenous components of blood and tissue in pregnancy.

Summary

1. Total α-amino nitrogen of plasma is decreased in pregnancy, rising to normal levels 24 to 72 hours post partum.

2. Serial determinations made on normal pregnant women and on patients with toxemia of pregnancy showed no apparent difference in plasma levels of α-amino nitrogen.

3. "Combined" α-amino nitrogen of plasma is unaltered by pregnancy or toxemia of pregnancy.

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THE ORAL USE OF A PHOSPHORATED CARBOHYDRATE SOLUTION IN NAUSEA AND VOMITING OF PREGNANCY

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NAUSEA and vomiting constitute one of the annoying problems of early pregnancy. Normally the condition responds to simple measures; occasionally, however, it can be a major complication requiring hospitalization.

Although many theories have been advanced to explain its etiology, there is no general agreement as to the method by which pregnancy leads to nausea.[1] Most authorities believe that psychic factors play an important role. Some observers[2, 3] have stressed the importance of hunger and an empty stomach, and have emphasized frequent small carbohydrate feedings. Although the mode of action is uncertain, the use of carbohydrate feedings may be considered a physiologic approach to treatment.

Recently claims have been made for the efficacy of a phosphorated carbohydrate solution* in the treatment of nausea and vomiting. The formula is stabilized at an optimal, physiologically adjusted hydrogen-ion concentration. It has been considered desirable to run a controlled clinical test to determine its effectiveness during pregnancy.

The preparation was introduced into therapeutics by Bradley[4] for the treatment of epidemic vomiting in children. More recently it has been found of some value in the management of motion sickness, regurgitation of infants, and vomiting associated with certain acute infections.[5]

Method

Cases of nausea or vomiting seen in the obstetrical practice of one of us (A. B. C.) were the subjects. All patients were given similar instructions with regard to diet on their first prenatal visit, which was usually during the first trimester of pregnancy. If nausea and/or vomiting were prominent annoyances, the patients were selected for this study.

The alternate case method was used. Regardless of severity or other status, alternate patients were given a phosphorated carbohydrate solution or a placebo solution in the same type bottle, and with the same green color to the liquid.

The patient was told to take two teaspoonfuls of medicine on arising in the morning *without* any additional liquid. If necessary, this dose was increased up to two tablespoonfuls. Repeated dosage was suggested as required

*The product used was Emetrol, which was furnished through the courtesy of Kinney & Company, Columbus, Ind. Emetrol is a solution of invert sugars (57 per cent total solids) and orthophosphoric acid with suitable stabilizers and flavors.

throughout the day and in most instances was taken shortly after the midday meal. In those cases in which nausea persisted throughout the day, medicine was taken as frequently as four or five times daily. No other medication for control of the nausea or vomiting was prescribed at the same time.

In interpreting results patients were classified according to four general groups. "Marked improvement" was used to signify complete or nearly complete cessation of the symptoms with repeated dosage. "Some improvement" was used to indicate a significant lessening of nausea or vomiting either in amount or frequency, yet not complete relief of symptoms. A third group showing little or questionable benefit was classed as of "little value." A small number of patients stated the medication used made the condition worse. The trial period was three days of consistent use, the patient recording in her own words her reactions at the end of that time.

The placebo solution consisted of carboxymethylcellulose, glycerin, saccharin, flavor, pure food color, and preservative in an aqueous base. In comparison with the original phosphorated carbohydrate solution it was slightly less sweet but otherwise a reasonably comparable facsimile.

Results

The results are shown in Table I. As this indicates, in both groups there were women who reported improvement and some who claimed they were made worse. The phosphorated carbohydrate solution, however, produced marked improvement in 28.4 per cent of cases. In some instances this was dramatic. The control solution proved "markedly" helpful for one patient. The phosphorated carbohydrate solution was of "some" help in 50.4 per cent of cases, while the control solution was reported helpful to only 14.8 per cent. These figures can be summed to show the comparison between those who were definitely helped ("some" and "marked" improvement) and those not definitely helped ("made worse" and of "little value"), Table II. Since the standard deviation is 6.3 per cent, one may regard the phosphorated carbohydrate solution used as having been of definite assistance in the control of nausea and vomiting of pregnancy in a significant proportion of the cases treated.

TABLE I

	NO. CASES	PER CENT
Phosphorated Carbohydrate Solution Group (123 Cases).—		
1. Marked improvement	35	28.4
2. Some improvement	62	50.4
3. Little value	22	17.9
4. Made worse	4	3.3
Control Group (122 Cases).—		
1. Marked improvement	1	0.8
2. Some improvement	18	14.8
3. Little value	93	76.1
4. Made worse	10	8.2

TABLE II

	DEFINITELY HELPED		NOT DEFINITELY HELPED		
	NO. CASES	PER CENT	NO. CASES	PER CENT	TOTAL
Phosphorated carbohydrate solution	97	79	26	21	123
Control solution	19	16	103	84	122
Totals	116	(47%)	129	(53%)	245

Those who reported that the condition was aggravated stated that it was because the solution was either too sweet or more frequently that they disliked the taste of peppermint. No other unpleasant side effects were reported.

When the material being tested (either the phosphorated carbohydrate solution or the placebo) proved of little value, other measures were employed after the third day and included the use of such medications as phenobarbital, pyridoxine hydrochloride, Dramamine, and Dexedrine Sulfate.

Comment

The value of a phosphorated carbohydrate solution in the treatment of nausea and vomiting of pregnancy was demonstrated. Because of differences in our basis for classification of results and the length of time the patients were kept on the medication prior to final decision as to benefit or lack of benefit, a comparison with the work of Anspaugh or Finch is not justified.

Other observers have reported marked improvement with the use of Dexedrine and antihistamines; we have found these preparations of some value but in far lower proportions of cases than reported in the papers of Anspaugh[6] and Finch.[7] The time needed to obtain a favorable result in this series was usually brief, generally after the first or second day of use. It was difficult to maintain patients on the medication in those instances in which the first few doses failed to result in definite improvement of the condition.

It is believed that a phosphorated carbohydrate solution has a definite place among the various medications commonly employed in the control of nausea and vomiting of early pregnancy. Its advantages are that it is free of annoying side effects, is a safe and physiologic agent, neither stimulates nor depresses the individual, and is relatively inexpensive. Further, its value for a given patient can be readily appraised by the physician in a minimum of time.

Summary

1. A phosphorated carbohydrate solution was used for the control of nausea and vomiting of pregnancy in a series of 123 cases. An alternate series of 122 patients requiring treatment served as a control.

2. This preparation produced measurable improvement in a significant proportion of such cases. Such improvement was usually noted within the first twenty-four hours of treatment and was unattended by any annoying side effects.

3. A phosphorated carbohydrate solution is recommended as a medication worthy of further clinical trial and use in the treatment of nausea and vomiting of early pregnancy.

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ACUTE PULMONARY EDEMA IN PREGNANCY

With Report of Case Responding to New Form of Therapy

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ACUTE pulmonary edema is one of the most dramatic complications of pregnancy. Statistical evidence concerning its incidence and effect on mortality during pregnancy is meager. It is generally considered a frequently fatal complication in all but its mildest forms; therefore, prompt recognition and successful treatment of this syndrome may be lifesaving for both mother and fetus.

Recent laboratory and clinical investigations have demonstrated the efficacy of a new form of therapy for acute pulmonary edema.[1] Although this syndrome is primarily of interest to the internist, and early reports have been directed to him, it is felt that the obstetrician should be familiar with current thought on this subject, since he must recognize and treat this urgent complication when it occurs. It is the purpose of this paper to discuss the pathogenesis and conventional therapy of pulmonary edema, and to examine the literature pertaining to this condition as a complication of pregnancy. In addition, the successful use of alcohol vapor therapy in a pregnant patient with the most severe form of acute pulmonary edema will be discussed in detail.

Review of the Literature

Jensen[2] presents an excellent review of the subject of acute pulmonary edema in pregnancy, and credits P. Barrere with reporting the first case in an early seventeenth century publication. An engrossing verbatim translation of a report by Michael Peter in 1872 is given. The French authors in the latter part of the nineteenth century established the entity of acute pulmonary edema and attempted its classification. American literature of the same period presents individual case reports, the earliest of which were by Curtin and Mann in 1879.

There have been isolated case reports and reviews of published cases in the American literature since the start of this century. McIlwraith and Scott[3] reviewed the literature from 1903 to 1918 and added two cases. In the third decade of this century, Bonn,[4] Schatz,[5] King,[6] Rudolph,[7] and Reid and Teel[8] presented additional case reports. Lindeboom[9] and Jones[10] reported other cases in 1948 and 1951.

Examination of the cases presented reveals that acute pulmonary edema may occur at any period of gestation, from conception to the postpartum period. In a compilation of cases, Jensen[2] has shown that approximately 56 per cent occurred during labor and in the twenty-four-hour period immediately following. An increased incidence of maternal mortality with primiparity, and with combined aortic and mitral valvular lesions was noted.

The statement that an increased incidence of acute pulmonary edema occurs in pre-eclampsia and eclampsia is repeatedly found in the literature of the past twenty years. This appears to be based upon the reports of Slemons[11] and King.[12] Analysis of their reports does not substantiate this conclusion. Slemons

reported seven cases of eclampsia without convulsions and records autopsy findings of pulmonary edema. A review of these cases fails to reveal any symptomatology consistent with acute pulmonary edema during life, so that the condition was recognized only as a postmortem (probably terminal) finding. King, reviewing the use of barbiturate therapy in 30 eclamptic patients, reports the development of acute pulmonary edema in four. This represents far less than the repeatedly quoted incidence of 30 per cent in toxemia of pregnancy; moreover, the question of anesthetic aggravation is raised by the author in connection with these cases.

The generalized edema of a toxemic patient poses a difficult differential diagnosis between that of pulmonary râles on that basis and that of cardiac failure. Hamilton[13] infers that a differential diagnosis based upon physical examination is possible; yet Reid and Teel[8] do not draw this conclusion in their reported series, although the same patients were under observation. Clinical experience indicates that Hamilton's criteria represent an oversimplification.

There is an apparent, but inadequately documented, increased incidence of acute pulmonary edema in toxemic patients, even though this is not an essential predisposing factor. Regarding previously existing heart disease as a predisposing cause or contributing factor, the same conclusion is drawn, again without the benefit of extensive data. There is an apparent slight increase in incidence with pre-existing cardiac disease as reported by Jones,[10] and Reid and Teel.[8] On the other hand, Lindeboom reports cases in which no pre-existing cardiac disease or toxemia was apparent. Certain cases may fall into the category of idiopathic myocardiopathy or, "postpartum heart disease"; however, since the nature of this syndrome is still undefined, it will not be discussed herein.

The incidence of acute pulmonary edema in pregnancy as reported by Hamilton[13] was five cases in approximately 20,000 deliveries (0.025 per cent). In a series of over 100,000 births at Cook County Hospital from 1930 to 1951, one maternal death due to acute pulmonary edema, and two other cases of severe pulmonary edema were noted.[14] A few mild cases might have been overlooked in this period of time. Browne[15] in 1942 reviewed 239 cases of heart disease in pregnancy without observing any with acute pulmonary edema. Chesley[16] in 1947 reviewed 218 cases of heart disease apparently without pulmonary edema. Ross[17] in 1948 reviewed 54 deaths in cardiac patients and found no acute pulmonary edema. Jones[10] in a review of 352 cases found four cases of pulmonary edema, and Fitzgerald[18] in a review of 1,030 cardiac cases reported no cases of acute pulmonary edema.

It is evident that acute pulmonary edema in its severe form is a rare obstetrical complication.

Pathogenesis

Acute pulmonary edema is a clinical syndrome resulting from a relatively sudden transudation of a large quantity of fluid of high protein content into the pulmonary alveoli and tracheobronchial tree. It is manifested by moist and dry râles of variable degree, usually throughout all lung fields, foamy expectoration (frequently bloody), and a variable degree of respiratory and circulatory embarrassment. Probably some edema occurs concomitantly with "pulmonary congestion"; however, if this is so, the manifestation is subclinical. Microscopic "edema" is a postmortem finding in a large percentage of patients who die from various causes. As such, it bears no specific relationship to the syndrome under discussion. *All that "rattles" is not pulmonary edema.*

The term "acute pulmonary edema" has been widely used interchangeably with "left ventricular failure." This usage is deceptive and certainly unwarranted. The syndrome of acute or paroxysmal pulmonary edema may be associated with various lesions of the lungs, tracheobronchial tree, and the

central nervous system, as well as the heart. Moreover, those cardiac conditions that may lead to its production either are confined to nor necessarily involve failure of the left ventricle. Numerous methods for the experimental production of this syndrome and the variable physiologic alterations consequent to its development have been described by others.[19, 20] The basic mechanism by which it is produced in man is not fully understood. Unitarian theories of pathogenesis fail to explain its occurrence under physiologically diverse circumstances. It is probable that nervous reflexes, as well as mechanical derangements of the heart and blood vessels, operate to a variable degree in most cases; individual factors only rarely, if at all. As has been emphasized by Luisada, any factors leading to high pressure in the pulmonary circulation, or dilatation or increased permeability of the pulmonary capillaries may precipitate an attack.

Physiologic alterations in pregnancy that tend to favor the production of pulmonary edema are: (1) increase of blood and plasma volume; (2) relative decrease of plasma proteins; and (3) increase of cardiac work (increased venous return and cardiac output). In the presence of toxemia, the additional burden of hypertension upon the heart and increased capillary permeability may be added to those already mentioned. In the pregnant woman with organic heart disease, the problems related to this complication are added.

Treatment

The conventional therapy of acute pulmonary edema in pregnancy has been similar to that used in the nonpregnant, with the additional advice by some that pregnancy be terminated. The recommendations in this latter matter are various. Whereas the advent of pulmonary edema is thought by some to be an absolute contraindication to continuing pregnancy, others suggest expectant management if the fetus is near viability. If acute pulmonary edema occurs in a patient who has antecedent heart disease with prior episodes of failure or borderline compensation, pregnancy should be avoided. In patients with good reserve, the indications for preventing pregnancy are not as well established. Since, as shown above, acute pulmonary edema is an apparently rare occurrence in pregnant women even with antecedent heart disease, the possibility of its occurrence should be weighed no more than the threat of congestive failure of the more common type, or toxemia. It has been suggested that all patients be delivered in Fowler's position.[7] Although probably unnecessary in the routine case, this suggestion may have merit where complicating factors increase the likelihood of paroxsymal pulmonary edema during delivery. It should be emphasized that all published advice on this problem is based on inadequate data; therefore, each case must be evaluated individually. The very fact that acute pulmonary edema may occur at almost any time during gestation, during labor, or in the postpartum period sheds doubt upon absolute therapeutic generalizations with respect to obstetrical management of this incompletely understood problem.

Most of the conventional therapeutic measures used may be relatively or absolutely contraindicated under certain circumstances. Morphine, the most widely accepted, may be deleterious in cases complicated by shock or cerebral lesions; moreover, large intravenous or hypodermic doses are thought by some to be detrimental to the fetus. Recently, respiration in the newborn was found to be definitely delayed in cases where morphine was administered for analgesia during labor.[21] The same objections apply to barbiturates and chloral hydrate. Aminophylline, venesection, mercurials, and positive-pressure respiration are contraindicated when shock is present or impending because they decrease venous return. Rapid-acting digitalis preparations, e.g., ouabain, strophanthidin, lanatoside-C, are of questionable value and may be detrimental. Other digitalis preparations with delayed onset of action are obviously of no value in the acute attack and are more properly reserved for the selected recovered patient.

Recognizing the limitations of conventional therapy of acute pulmonary edema, Luisada, Goldmann, and Weyl[1a, b, c] have studied the use of ethanol-oxygen vapor by inhalation in the treatment of this syndrome as occurring in a variety of medical and surgical conditions. The results of their studies indicate that alcohol vapor exerts a favorable action, particularly in the acute paroxysmal variety of pulmonary edema. Its principal mode of action is apparently as an antifoaming agent. A report of ethanol-oxygen vapor therapy in a case of acute pulmonary edema complicating labor follows.

Report of a Case

A 43-year-old Negro woman was admitted to Cook County Hospital on Jan. 9, 1951, because of hypertension complicating pregnancy. A gravida xv, para xii, she offered no complaints. Hypertension had been noted during two earlier pregnancies; however, no interim examinations had been performed. Physical examination revealed an obese woman with blood pressure of 230/140; pulse 84; temperature 98.6° F.; and respiration 20. The size of the uterus was consistent with a nine months' gestation. Fetal heart tones were 152.

Laboratory findings on admission were: Hemoglobin 50 per cent (7.8 Gm.), red blood cells 3.12 million, white blood cells 14,200; traces of acetone and protein in the urine; nonprotein nitrogen 19 mg. per cent; serum protein 5.7 Gm. per cent (albumin 3.1 Gm. per cent, globulin 2.6 Gm. per cent); blood uric acid 6.1 mg. per cent; Kahn test negative. A chest film was reported as within normal limits. The four-lead standard electrocardiogram was interpreted as within normal limits, with left axis shift.

Shortly after admission, the patient, considered to have pre-eclampsia, was placed on a modified Stroganoff regime. This included the periodic use of morphine sulfate, magnesium sulfate, and 25 per cent dextrose in water intravenously, and ammonium chloride by mouth. By January 10, the patient's blood pressure dropped to 154/92 and the fetal heart tones could not be heard with certainty. At 1:15 P.M., spontaneous rupture of the fetal membranes was noted. A vaginal examination revealed a cephalic presentation, the presenting part floating, and the cervix not dilated.

While lying supine upon a delivery table following the examination, the patient complained of flushing and a choking sensation. She became severely dyspneic, cyanotic, and developed acute pulmonary edema of the greatest severity, continuously emitting a copious amount of pink froth from the nose and mouth. At 8:30 P.M., the patient's head was elevated to about 40 degrees and positive pressure oxygen by mask was instituted. Successively, morphine sulfate 30 mg., aminophylline 0.5 Gm., atropine sulfate 0.5 mg., Sodium Amytal 0.5 Gm., and Digalen (one cat unit) were administered intravenously within 15 minutes from onset. At 9:10 P.M. (40 minutes after these measures were completed), frothy sputum was still emitted in copious quantity from the delirious patient's mouth.

Administration of ethanol-oxygen vapor was then started per mask, utilizing a standard anesthesia apparatus with 35 per cent alcohol in the "ether container." It was necessary to remove the mask frequently to permit removal of collected foam. Improvement was prompt, dramatic, and progressive. Within 15 minutes, the foam became more liquid in character so that more effective expectoration was possible. Within 20 minutes, the patient was no longer in severe distress. At the end of 30 minutes, she was able to sit up and speak clearly, although with some effort. Bubbling and crepitant pulmonary râles were markedly reduced in quantity. No further alcohol vapor was given. Approximately seven hours later, the patient spontaneously delivered a female infant who required tracheal catheterization and oxygen.

On January 15, no further cardiorespiratory distress had occurred. The patient's blood pressure was 185/110 and the pulse, 82. The conjunctivae were pale. A Grade 2 apical systolic murmur and Grade 3 hypertensive retinopathy (Keith-Wagener) were present. Otherwise, the findings were noncontributory. Seven weeks post partum, the patient's status was re-evaluated at the Cardiac Clinic. Although free of complaints, she was found to have a blood pressure of 230/120 and pulse of 88 in both arms; the apex was 4 cm. outside of the left midclavicular line, and a trace of pretibial edema was present. Fluoroscopy revealed left ventricular and probably also left auricular enlargement. A twelve-lead electrocardiogram, including standard and unipolar extremity and chest leads, was interpreted as being

abnormal and consistent with left ventricular hypertrophy and "strain." Final diagnosis: hypertensive cardiovascular disease and term pregnancy. The infant is free of illness, but somewhat retarded in growth and development.

In summary, a 43-year-old Negro woman with asymptomatic hypertensive cardiovascular disease and term pregnancy developed acute paroxysmal pulmonary edema of the utmost severity. After an unsuccessful trial of conventional forms of medical therapy, oxygen-alcohol vapor was administered and followed by prompt and dramatic recovery. Spontaneous delivery of a viable infant occurred seven hours later.

Comment

The question as to whether a superimposed toxemia of pregnancy was present in this patient cannot be answered with certainty. The absence of peripheral edema or history of extraordinary weight gain, the presence of only a trace of proteinuria, and only borderline elevation of blood uric acid militate against this diagnosis. We feel, if present at all, the toxemic component was negligible.

Factors other than the general mechanisms discussed above that may have predisposed to the production of acute paroxysmal pulmonary edema in this case are: (1) the assumption of the lithotomy position immediately prior to onset, thereby stimulating reflex nervous and humoral mechanisms, and (2) the use of 25 per cent glucose in water intravenously and large doses of intravenous magnesium sulfate, both of which may temporarily increase blood volume.

It is noteworthy that there was no recurrence of symptoms during delivery and that symptoms of congestive failure were not present in the postpartum period.

According to the impression of several members of the house staff present during the attack, alcohol vapor therapy was the critical measure in this patient's recovery. This viewpoint is supported by the fact that the patient's condition remained unimproved after an interval sufficient to permit the maximum effect of other therapy, and that prompt and progressive amelioration followed the use of ethanol-oxygen vapor. Digalen could not have been active until a number of hours after recovery. That the favorable outcome might have been the result of the alcohol therapy added to a beneficial, but independently inadequate, effect of the other drugs, can only be a matter for speculation.

Studies have demonstrated that the amount of alcohol absorbed in the course of this treatment is far below levels of intoxication.[1, b, c] It is extremely unlikely that such levels can produce an important effect upon the fetus. On the other hand, large doses of morphine, hypnotics, anesthetic, as well as venesection, can have a deleterious effect. To what extent they were responsible for the poor condition of the newborn in this case cannot be determined.

Studies of ethanol-oxygen vapor therapy have failed to establish any definite contraindications to its use,* alone or in combination with other measures.[1, b, c] Subsequent to treatment of this patient, a simpler technique,† utilizing a nasal catheter and 95 per cent alcohol, has been used with consistently good toleration (better than the mask), and excellent results in nonpregnant patients.[1, b, c] Either the mask or catheter technique is easily employed with equipment that is readily available in the average birth room or maternity hospital.

Summary and Conclusions

1. Severe acute paroxysmal pulmonary edema is a rare complication of pregnancy which seriously threatens the life of mother and fetus. The advent of this syndrome demands prompt and individualized treatment.

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*Theoretically ethanol-oxygen vapor should not be given to patients taking tetraethyl thiuram disulfide (Antabuse).[1, c]

†Goldmann and Luisada have reported excellent results with the following simplified technique: 95 per cent ethyl alcohol is placed in the humidifier of standard oxygen equipment, and the vapor formed by bubbling oxygen through the alcohol is administered by nasal catheter. The oxygen flow is gradually raised to 7 L. per minute, as tolerated.

2. The theories of pathogenesis and methods of treatment of acute pulmonary edema are discussed with particular reference to its occurrence during pregnancy.

3. The obstetrical literature concerning this subject is reviewed. A case of acute pulmonary edema of the severest degree, occurring in a hypertensive patient at term, and treated by ethanol-oxygen vapor by inhalation, after an unsuccessful trial of conventional therapy, is reported for the first time in obstetrical literature.

4. Other studies have shown that ethanol-oxygen vapor by inhalation is apparently free of contraindications. Its use, independently or in combination with other indicated measures, is recommended in the treatment of acute pulmonary edema occurring during pregnancy.

Addendum.—Since completion of this paper, an additional case of acute pulmonary edema occurring during labor has been treated with prompt success at Cook County Hospital. The attack occurred in a patient without antecedent heart disease, but with definite preeclampsia. Although not as severe as the attack described above, it also commenced while the patient was in the lithotomy position. The role of ethanoloxygen vapor inhalation in the patient's recovery cannot be clearly evaluated since intravenous aminophylline was also given.

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ABDOMINAL PRURITUS IN PREGNANCY

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PRURITUS of the abdominal skin in pregnancy has received little or no attention in the textbooks and monographs dealing with dermatologic complications of gestation. Recourse to several of the widely used texts reveals no mention of this problem. Actually, pruritus is a symptom and not a disease diagnosis. It is, however, a common, persistent, and distressing symptom. By common usage the medical profession has come to regard pruritus as almost a disease entity in itself.

Like hiccough, heartburn, or sunburn, itching is one of the seemingly mild symptoms which seem humorous to observers but which may be desperately serious to the patient. No physician who has treated a refractory case of pruritus is likely to view the symptoms lightly. Indeed, the few moderately effective drugs available for this purpose are so limited in their application and so uncertain in their action that any new treatment for the relief of itching is certain to attract attention. Not infrequently, relief from uncontrolled pruritus is obtained by the patient only when the skin is severely traumatized by sharp objects. Frank pain then replaces the pruritus and brings relief to the tormented patient from the less desirable of the two discomforts. Symptomatic relief of itching is of considerably more importance to the patient than etiological eradication, which can be accomplished in a more leisurely way after the patient has been rendered comfortable.

Most commonly in pregnancy pruritus is limited to the vulval area and many reports have covered this phase of the dermatologic complications of pregnancy. Aside from the common specific sources of pruritic lesions there still remains a group without demonstrable cause which is commonly referred to as "essential," "psychosomatic," or "idiopathic." Often the pruritic symptom-complex in this instance is on the basis of conditioned reflex activity and the itch-scratch-itch vicious cycle may persist after the instigating factor has been brought under control.

The present clinical report investigates itching or pruritus of the abdominal skin which occurs as a complication of pregnancy unrelated to specific dermatoses or to itching elsewhere in the body. It is a local rather than a systemic problem.

Method of Study

Alternate patients with uncomplicated pruritus abdominalis during pregnancy applied one of two antihistaminic topical preparations to the abdominal skin to evaluate the effectiveness of this form of therapy in the control of

itching. Thephorin* was used on alternate subjects as a 5 per cent ointment or lotion (35 subjects), and Pyribenzamine† 2 per cent cream on a similar group (30 subjects) chosen alternately with the Thephorin group. The response to this therapy was so clear cut that it was found possible to tabulate the results as either "improved" or "not improved." The cream, lotion, or ointment was applied locally to the anterior abdominal skin as often as the symptoms warranted therapy.

Results

The results of this study are shown in Table I. In a group of 365 successive private obstetric patients, covering more than two years, the incidence of uncomplicated abdominal pruritus during pregnancy sufficient to warrant complaint by the patient was found to be 17.8 per cent. The effectiveness of both antihistaminic drugs was found to be approximately the same; nine out of ten patients with pruritus abdominalis responded with complete disappearance of the itching within ten to fifteen minutes after application. It was usually not necessary to apply the medication more than two or three times daily. The lotion seemed to have more satisfactory esthetic qualities and revealed a higher degree of patient acceptance. The incidence of the symptoms appears to be less during the first trimester than during the second and third trimesters of pregnancy.

To a great extent the highest peak of incidence occurs during the warm, humid months of the summer season, but instances of severe or moderately severe abdominal pruritus have occurred in patients at any time of the year including the cold winter months. An attempt has been made to establish some relationship between temperature, humidity, type of undergarments and abdominal supports worn, but no clear correlation of these factors with the incidence or severity of abdominal pruritus has been established. An attempt to establish some relationship between the presence of striae gravidarum and pruritus of the abdominal wall is doomed to failure since 90 to 100 per cent of the patients in the last trimester of pregnancy revealed some "striae" (lineae albicantes gravidarum). In this sense, then, the relationship between abdominal pruritus and striae must of necessity be the same as the relationship between abdominal pruritus and pregnancy and no significant statistical evaluation would be of help in elucidating the problem. It does seem, however, that patients with marked striae gravidarum changes do have more

TABLE I. RESULTS OF TREATMENT IN PRURITUS ABDOMINALIS BY TOPICAL ANTIHISTAMINICS IN 365 PREGNANT WOMEN

TRIMESTER OF PREGNANCY	NUMBER OF SUBJECTS			RESULTS IN SUBJECTS WITH PRURITUS ABDOMINALIS							
				THEPHORIN (LOTION 18, OINTMENT 17)				PYRIBENZAMINE			
				IMPROVED		NOT IMPROVED		IMPROVED		NOT IMPROVED	
	WITHOUT PRURITUS	WITH PRURITUS	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
First	42	3	7.0	2	100.	0	0	1	100.	0	0
Second	110	23	17.	11	91.7	1	8.3	11	100.	0	0
Third	213	39	15.	19	90.5	2	9.5	16	88.8	2	11.2
Total	365	65	13.	32	91.4	3	8.6	28	93.3	2	6.7

*Thephorin 5 per cent ointment and lotion (2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate) were supplied for this study by Hoffman-La Roche, Inc., Roche Park, Nutley 10, N. J.

†Pyribenzamine 2 per cent cream (N'-pyridyl-N'-benzyl-N-dimethyl-ethylenediamine monohydrochloride) was supplied for this study by Ciba Pharmaceutical Products, Inc., Summit, N. J.

severe pruritus abdominalis than do those with mild or moderate degrees of striae changes.

Histologically the striae are the result of separation of the connective tissue in the cutis and subcutis with tearing of the collagen fibers and formation of a rhomboid arrangement of the fibers resulting in a parallel disposition of the strands perpendicular to the striae. The elastic fibers are always torn and the retracted edges are found at the edge of the striae. The lymph spaces in these areas are compressed and arranged in a parallel manner. The epidermis in these cases appears to be somewhat thin and the deposition of pigment in the striae notable in brunettes and Negro women is real.

An attempt to correlate the incidence of pruritus of the abdominal skin with previous neuropsychiatric disorders was of little avail since the incidence of neuropsychiatric disorders in the past history of young pregnant women is, of necessity, small. Actually, but two of the 365 women in this study revealed a past history of neuropsychiatric disorders requiring treatment.

Lack of cleanliness was considered as another cause of abdominal itching but this again was not felt to be a significant factor in this series since all 365 women were private patients and were reasonably fastidious during pregnancy.

In common with pruritus elsewhere in the body, particularly the vulva, the itching is usually worse at night and in the summer. Possibly this is due to lack of distraction from the annoying symptom during the night as well as to increased warmth and humidity under bedclothes. In all instances in this series the skin was not different in appearance from that of the controls except for occasional scratch marks. Patients with discrete dermatologic lesions of the skin during pregnancy were excluded from this study. Urticarial reactions in the skin were not seen as concomitant factors in the present study, and, when they were present, these patients were eliminated from the series.

Comment

In recent years interest in the antihistaminic drugs has increased greatly. The local antipruritic effects of these drugs has been demonstrated experimentally by Aaron, Peck, and Abramson,[1] among others. However, there is no complete agreement as to the exact degree of clinical effectiveness of the different members of this series of substances when applied locally in various dermatoses. The efficacy of topical antihistaminic substances for the relief of pruritus has been demonstrated clinically by Perry,[2] Feinberg and Bernstein,[3] Sulzberger, Baer, and Levin,[4] and others. The use of antihistaminic agents for various forms of allergic disease is now well established.[5] Friedlaender and Feinberg[6] showed that the local application of a solution of antihistaminic agent produces significant reduction in the whealing reaction produced by application of histamine to the skin. In contrast, oral administration of the antihistaminic agent has but a slight inhibitory effect on experimentally produced histamine wheals. This observation, therefore, suggests that the topical application of an antihistaminic substance may be more effective than oral administration in inhibiting symptoms which have their origin in local tissue changes.

The mode of action of antihistaminic agents is not clearly known. Several theories have been proposed: (1) that they prevent the release of histamine in tissues; (2) that they neutralize histamine; (3) that they block the action of histamine. The last theory is accepted by most authorities. It is claimed that the antihistaminic drug combines with the tissue cells at the site of action of the histamine rather than with the histamine itself. Thus the pharmaco-

logic effects of histamine are prevented by blocking the union of histamine with the tissue cells. These theories, of course, assume that the itching in most dermatologic disorders has some relationship to histamine and this factor has still to be established.

Preliminary investigations have shed some light on neurologic pathways and centers concerned in the sensation of itching. Koenigstein[7] used dogs which exhibit every manifestation of pruritus when they are injected intravenously with thalassin (an alcoholic extract of the tentacles of Actinia). Such dogs offer an experimental approach to the study of transmission and control of itch stimuli. Morphine can be injected intracisternally in cats with similar pruritic effects. This pruritic action of morphine is not unexpected since it is known that morphine hardly influences persistent itching and that the use of morphine parenterally is not infrequently associated with itch reactions. Despite controversy, the weight of evidence suggests that pruritus and pain are distinctly different sensations and are represented in the brain in separate centers. Sympathetic fibers play a considerable role in realization of the itch-scratch reflex when such a sensation is peripherally induced. In other cases where the sensation of itching is centrally induced, as by intracisternal injection of morphine, other neurological mechanisms are involved. Koenigstein believes that the scratch center is located in the medulla oblongata and is bounded by the auditory nuclei and the corpora restiformia.

In centrally induced pruritus topical applications are likely to be ineffective. Oral antihistaminic therapy, however, may be helpful. Pruritus may be a manifestation of some internal disorder but may be entirely conditioned through psychogenic influences. Wiener[8] includes in the index of his book more than a dozen organic diseases under the heading "pruritus." Yet he is quick to point out that mental reactions are very common contributory factors to this disorder and that in some conditions the itch is more violent when the patient is excited and is mitigated when the patient is calm. It has been reported that some relief of symptoms can be obtained by local application of any cooling agent such as calamine lotion, alcohol, or ether. Attempts to desensitize the patient to histamine have been successful in a few instances and this would indicate that such patients might have been relieved by systemic administration of antihistaminics or by local application of the same. Shelmire[9] has employed an antihistaminic topically in 455 cases of dermatoses. Results were carefully evaluated by the use of placebo controls. Invariably patients found greater relief from topically applied antihistaminic therapy than from the control medication. An interesting finding was the discovery that patients with lesions of several years' duration obtained at least as much benefit as those in whom the dermatosis was of short duration. McGavack and associates[10] reported the use of local, topically applied antihistaminics in strengths of 2 per cent and 5 per cent, which provided complete relief in 32 of 56 cases in this series, and partial relief in an additional 16.

Several useful antihistamine compounds have been developed, most of which are phenolic ethers and derivatives of ethylenediamine. When administered to patients, all produce similar results and differ only in minor aspects of side effects and dosage. Oral administration is the most satisfactory route for production of systemic effects. However, on a local pruritic state such as abdominal pruritus in pregnancy, topical administration of the agent in use would seem helpful, from both a psychologic and therapeutic standpoint. Application of the drug in ointments and creams often relieves allergic skin involvements with fewer side effects.

The pharmacology of antihistamine compounds has been reported rather extensively by Loew[11] and will not be considered here.

Summary

Uncomplicated abdominal pruritus during pregnancy was found in 65 out of 365 pregnant women, an incidence of 13 per cent. Two antihistamine drugs applied topically—Thephorin and Pyribenzamine—were effective in controlling this symptom in nine out of ten patients.

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DOUBLE UTERUS AS AN ETIOLOGICAL FACTOR IN REPEATED ABORTION: INDICATIONS FOR SURGICAL REPAIR

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DOUBLE uterus of various degree is sometimes found in situations suggesting its importance as an etiological agent for various gynecological complaints. Recent experience has suggested that in properly selected cases plastic repair of the double uterus may be indicated. The concept of plastic repair for a variety of complaints is not new. Ruge[1] in 1884 first reported the excision of a uterine septum in a woman who had had two abortions. She subsequently carried to term. The procedure was popularized by Paul Strassmann[2] who unified a bicornuate uterus through the anterior cul-de-sac in 1907 and subsequently performed 17 unifications by a procedure which bears his name. Recently Erwin Strassmann[3] has been able to collect 114 such operations carried out over the last 70 years. These have been undertaken for habitual abortion, dysmenorrhea, menometrorrhagia, sterility, dyspareunia, and premature delivery. It is the purpose of the present paper to report a plastic repair for hematometra in a noncommunicating horn of a double uterus and to discuss the indication for plastic repair in repeated abortion as illustrated by five cases.

Miller[4] has reported a case with hematometra of a rudimentary horn of a double uterus, but apparently the literature contains no case of a noncommunicating horn of a septate uterus as illustrated by the following case:

CASE 1.—S. B., No. 537474, was 14 years of age. The first menstrual periods in September and October, 1949, were painless. From then until she was first seen on May 11, 1950, the patient had had four additional periods at intervals of about six weeks but with increasing pain. The pain began on the second day of flow and lasted the entire five days. It became so severe it was incapacitating. The flow was of normal quantity. Spotting had occurred five days before the April menses but there had been no other intermenstrual bleeding. The general examination, except for mild hirsutism, was negative. The pelvic examination under anesthesia revealed a small cervix displaced to the left by a rubbery mass which presented in and obliterated the right fornix. It extended almost to the pelvic wall laterally. Neither the fundus nor ovaries could be identified but the left adnexal region seemed clear. The mass was estimated to be 15 mm. in diameter. A tense cyst of Wolffian duct origin was suggested by the examination.

An intravenous pyelogram revealed a normal left urinary tract but no obvious excretion of dye on the right after 45 minutes.

By cystoscopic examination no right ureteral orifice was visualized; the left appeared normal.

Exploratory laparotomy was carried out May 16, 1950. The right kidney fossa was empty. The mass was found to be an enlarged right horn of a double uterus. There was a

small amount of menstrual blood in the peritoneal cavity. There was no communication between the left and right horns. The septum was excised and the two cavities united (Figs. 1, 2, and 3). The patient was discharged on the tenth postoperative day.

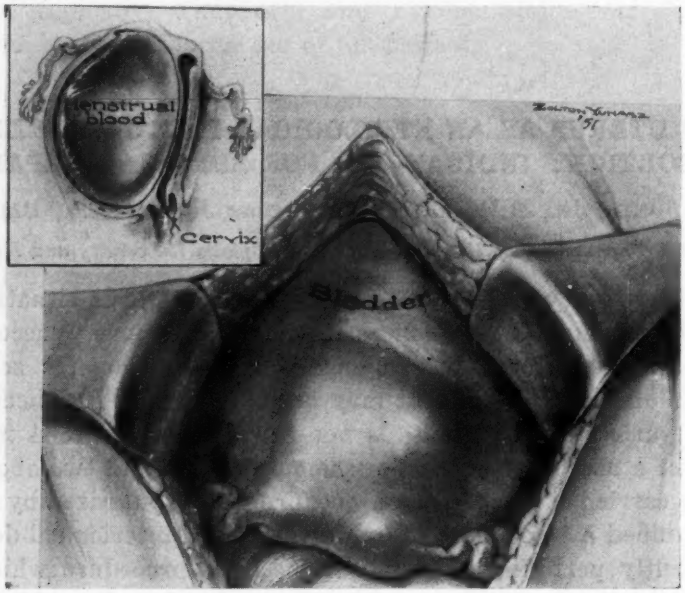

Fig. 1 (Case 1).—Appearance of uterus at operation. Inset shows a diagrammatic representation of a section of the uterus.

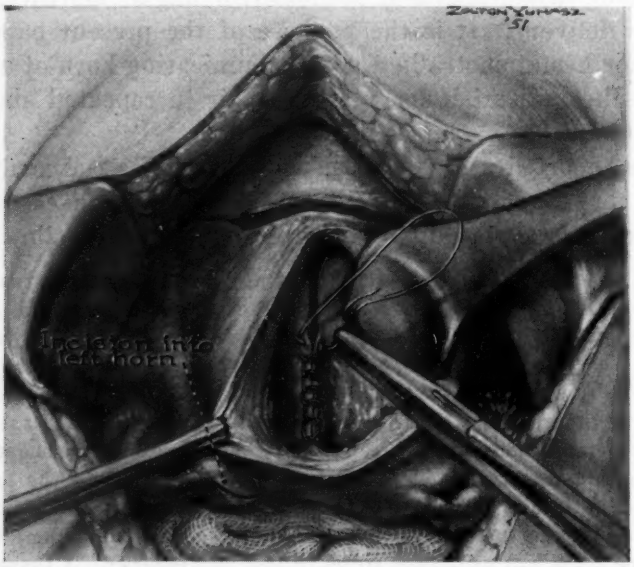

Fig. 2 (Case 1).—Plastic reconstruction of uterus by anastomosis of the two cavities after excision of the septum. This continuous locked stitch joining endometrium to endometrium was reinforced by interrupted myometrial sutures.

Two years after operation the patient is having menses every 2 to 3 months and has no pain. The pelvic examination reveals a uterus only slightly enlarged but symmetrical. A hysterogram taken 15 months after operation showed a globular but symmetrical uterine cavity (Fig. 4).

The successful unification of the two cavities in Case 1 led to a re-evaluation of the principle of plastic repair for repeated abortion.

A review of the material at our disposal makes it abundantly clear that the indication for repair in association with repeated abortion by no means rests simply upon the diagnosis of the double uterus. This congenital anomaly

Fig. 3 (Case 1).—The plastic reconstruction of the uterus is completed by a third layer of interrupted sutures, uniting the myometrium and serosal surface.

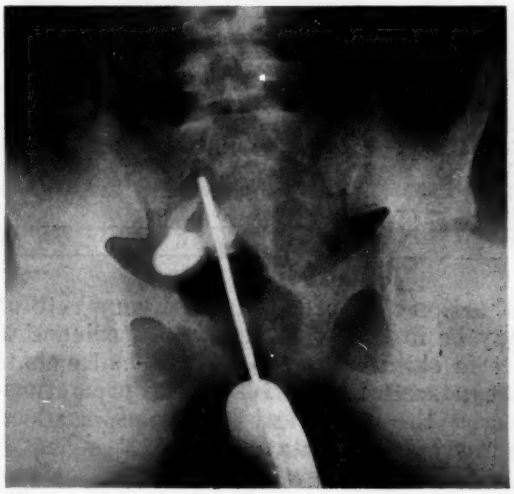

Fig. 4 (Case 1).—Hysterogram 15 months after the operative procedure illustrated in Figs. 2 and 3. The uterine cavity is enlarged and globular but symmetrical. No effort was made to demonstrate the tubes.

of various degree may be associated with term delivery in a relatively high percentage of cases. In repeated abortion, before repair is undertaken, the various metabolic and endocrine factors often associated with the condition must be excluded. In an effort to estimate the importance of double uterus in reproductive difficulties all such cases admitted on the obstetrical service

of the Johns Hopkins Hospital for the years 1936-1950, inclusive, have been reviewed. There were 21 such patients. Sixteen individuals fell into Group A with only minor reproductive difficulties, while 5 patients, who exhibited major problems, were placed in Group B.

By definition the latter group consists of those who have had no living children or who have had multiple abortions or premature deliveries.

In this small series there is therefore an over-all probability that about one of every four women with double uterus will have a serious reproductive problem. Tables I and II attempt to summarize the obstetrical histories of these two groups.

TABLE I. GROUP A

CASE NUMBER	TOTAL PREGNANCIES	TERM DELIVERIES	PREMATURE DELIVERIES	ABORTIONS	LIVING CHILDREN
A 1	4	4	0	0	3
A 2	1	1	0	0	1
A 3	1	1	0	0	1
A 4	2	2	0	0	2
A 5	1	1	0	0	1
A 6	1	1	0	0	1
A 7	3	2	0	1	2
A 8	7	3	3	1	4
A 9	1	1	0	0	1
A 10	1	1	0	0	1
A 11	2	2	0	0	1
A 12	1	1	0	0	1
A 13	4	4	0	0	2
A 14	1	1	0	0	1
A 15	2	1	0	1	1
A 16	2	2	0	0	2
Total	34	28	3	3	25

TABLE II. GROUP B

CASE NUMBER	TOTAL PREGNANCIES	TERM DELIVERIES	PREMATURE DELIVERIES	ABORTIONS	LIVING CHILDREN
B 1	6	0	6	0	1
B 2	5	1	0	4	1
B 3	4	0	0	4	0
B 4	1	0	0	1	0
B 5	2	0	0	2	0
Total	18	1	6	11	2

Although the abortion and premature delivery rate of about 10 per cent each in Group A may be in line with general experience with normal women, the loss of 4 of 28 term children emphasizes the more than normal obstetrical hazard. Nine cesarean sections in 31 term or premature deliveries (29 per cent) further emphasize the obstetrical handicaps, as does the occurrence of 2 compound and 2 transverse presentations.

Group B (Table II) of 5 cases illustrates the serious reproductive difficulties which may occur in association with double uterus. The single term delivery which occurred in 18 pregnancies, was apparently the result of a pregnancy in the right horn of a double uterus while the abortions resulted when implantation took place in the left. A somewhat similar case was reported by Oker-Blum.[5]

The incidence of abortion and premature delivery when Groups A and B are combined corresponds to that in other reports in the literature; although most series report all cases together and do not attempt to separate the patients with little or no trouble from those with serious difficulties.

Miller[4] collected 67 pregnancies in didelphic uteri with an abortion rate of 28.3 per cent. Smith,[6] in a careful analysis of 35 patients, noted an over-all abortion incidence of 19 in 81 pregnancies, or 23.5 per cent. Schauffler[7] reported on 11 patients, with 32 pregnancies and 17 abortions, giving an incidence of 53 per cent. Hoyt C. Taylor[8] reported upon 11 patients, 8 of whom were exposed to pregnancy. There were 12 pregnancies with 4 abortions, or 33 per cent. These figures must be compared with the combined figures of Groups A and B of 52 pregnancies in 21 women, resulting in 14 abortions, an incidence of 27 per cent. All of these figures are substantially higher than the 10 to 15 per cent usually quoted as the over-all population abortion incidence rate.

The 5 cases reported below have previous obstetrical experiences even more serious than those of Group B above. In 23 pregnancies there were no living children, one premature labor, and 22 abortions. All were patients on the Gynecological service at the Johns Hopkins Hospital and therefore are in addition to the 21 cases of Groups A and B. The case reports emphasize the importance of studying the endocrine and metabolic factors[9] as well as the anatomical features of double uterus.

Fig. 5 (Case 2).—Preoperative hysterogram showing widely divergent horns of a bicornuate uterus.

CASE 2.—V. B., No. 112288, was born in 1922. She married in 1942 and had miscarriages at 8 to 12 weeks in May, 1945, June, 1947, June, 1949, and June, 1950. Normal fetuses were reported. Bleeding required a dilatation and curettage after three of these. The patient was first seen July 25, 1950. On pelvic examination a double uterus was suggested. The basal metabolic rate was −3; cholesterol 155; Brucella agglutination negative. The basal temperature chart was normal biphasic. Endometrial biopsy on day 20 revealed a pattern corresponding to that day. The husband's semen was normal. A hysterogram revealed a questionable double uterus. The examination was repeated two days later with more definite findings (Fig. 5). An intravenous pyelogram showed normal kidneys and ureters, bilaterally. The patient was admitted to the hospital Sept. 11, 1950, when a repair of the uterus was accomplished as noted in Figs. 6, 7, 8, and 9. A postoperative hysterogram on Nov. 24, 1950, revealed a small globular cavity (Fig. 10).

On Dec. 27, 1951, a uterotubal insufflation was successful at 70/40 mm. of mercury. The last regular menstrual period was May 9, 1952. Chorionic gonadotropin titers and pregnanediol determinations were carried out as follows:

DAY AFTER LAST MENSTRUAL PERIOD	CHORIONIC GONADOTROPIN (INTERNATIONAL UNITS PER LITER BLOOD SERUM)	PREGNANEDIOL (MILLIGRAMS PER 24 HOURS)
29	3,000	–
35	60,000	7.4
63	200,000	–
83	120,000	–
104	48,400	–

In view of the normal values obtained, these studies were discontinued and no therapy of any kind advised. Pregnancy progressed normally and a normal female child was delivered by cesarean section on Jan. 24, 1952, as indicated by Figs. 11 and 12.

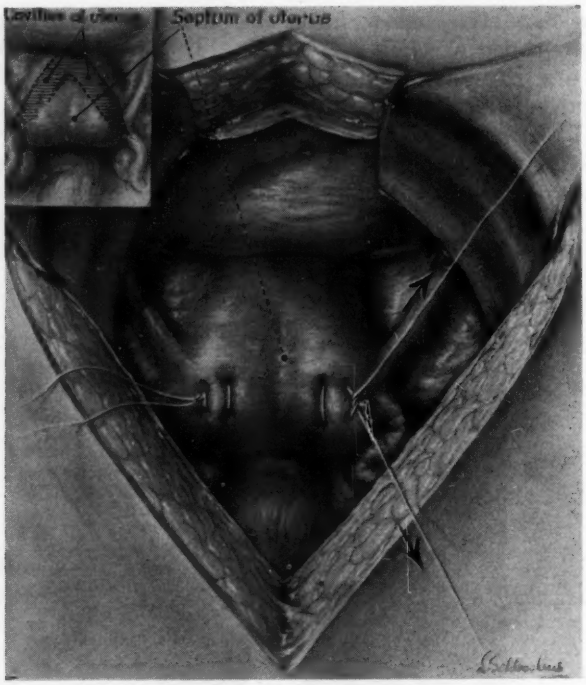

Fig. 6 (Case 2).—Appearance of uterus at operation.

Fig. 7 (Case 2).—The uterus bisected. After excision of wedge-shaped segment it was necessary to excise additional tissue to unroof each horn.

Summary and Interpretation.—This was a case of repeated abortion of normal fetuses with no discoverable abnormality in either partner except a double uterus. Plastic repair was followed by a term pregnancy and a living child.

CASE 3.—R. K., No. 53633, was born in 1915. A congenitally deformed right kidney was removed in 1935. She married in 1945, became pregnant promptly, and had four miscarriages in five years. All of these occurred by the second month and none revealed a recognizable normal fetus. The patient is a native of Israel and was extensively investigated there as well as in Europe and in many centers in the United States. She was known to have a double uterus, and the repeated abortions were attributed to this condition. She was first seen in May, 1950. There was a history of slight hirsutism which had progressed over a period of years. Menarche occurred at 12 years, and the menstrual interval was 28 days with a duration of 5 days. Her weight was 162 pounds; height 5 feet, 4 inches; blood pressure 128/90. There was marked blonde hirsutism, particularly of the lower extremities, but also present on the chin, upper lip, and anterior chest wall, both peripherally and around the nipples. The pubic hair had a masculine distribution. The Brucella agglutination was negative. The basal metabolic rate was −13; blood cholesterol

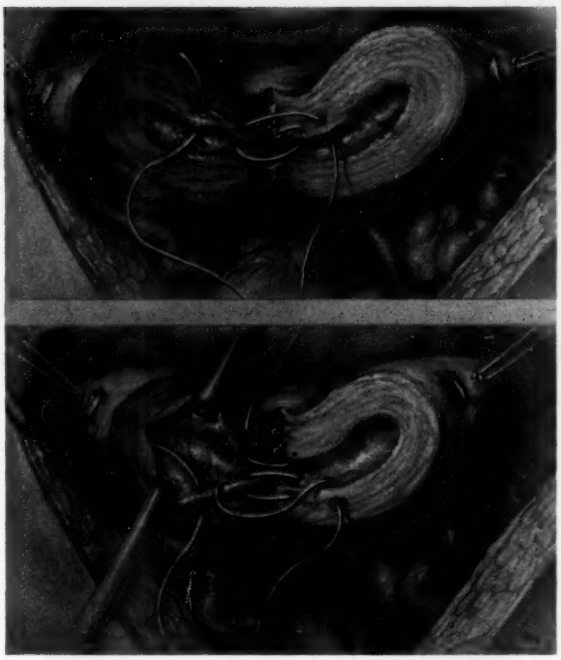

Fig. 8 (Case 2).—The anastomosis of the two halves of uterus. Two continuous sutures are used to join the endometrium.

was 258 mg. per 100 c.c.; glucose tolerance test: fasting 84 mg. per 100 c.c., one-half hour 120, 1 hour 116, 2 hours 92, 3 hours 72, 4 hours 80, 5 hours 80; urinary 17-ketosteroids were 20 mg. in 24 hours. A hysterogram (Fig. 13) showed a double uterus. Endometrial biopsy on the thirtieth cycle day showed a nonsecretory endometrium. This was also true on a repeated examination. The urinary pregnanediol excretion on day 21-22 was 1.2 mg. in 48 hours compared with a normal of at least 5.0 mg. A basal temperature chart showed a poor luteal rise.

Although there was a double uterus it was decided that there was also a serious luteal phase defect associated with lowered thyroid function and an adrenal abnormality. Consideration of surgical repair was postponed until these endocrine factors were corrected.

Therapy consisted of a high-protein, high-vitamin, 2,000 calorie diet and desiccated thyroid, 1½ grains per day. The patient's weight fell to 134 pounds by Sept. 31, 1950. On this day a blood cholesterol determination was 155 mg. per 100 c.c. and basal metabolic rate +30. She was allowed to discontinue contraception at this time and menstruated

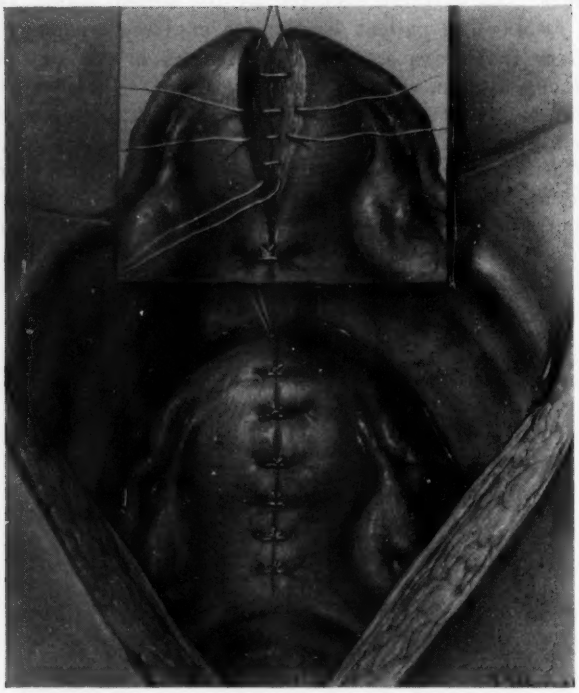

Fig. 9 (Case 2).—Inset shows second layer of sutures uniting the myometrium. The third layer unites the myometrium and serosa.

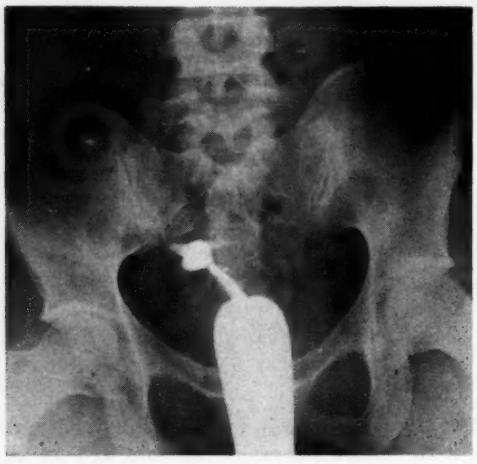

Fig. 10 (Case 2).—Postoperative hysterogram showing small but globular uterine cavity.

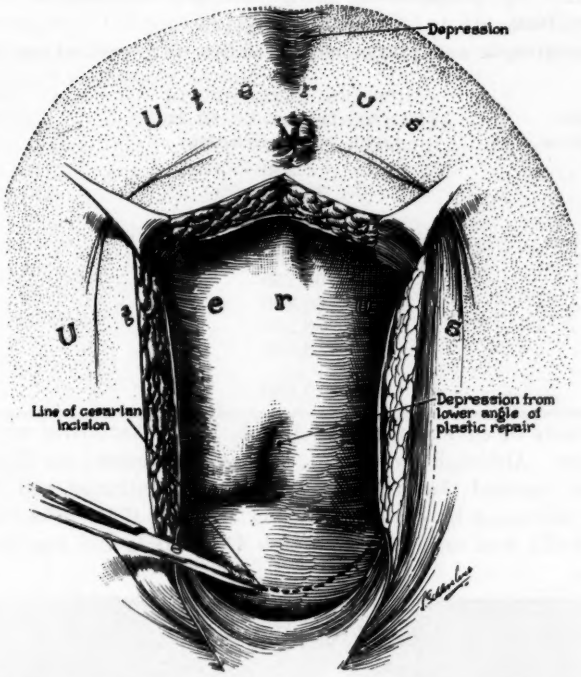

Fig. 11 (Case 2).—Appearance at cesarean section. There were three or four depressed areas along the line of repair. None of these areas were thin enough to suggest imminent rupture.

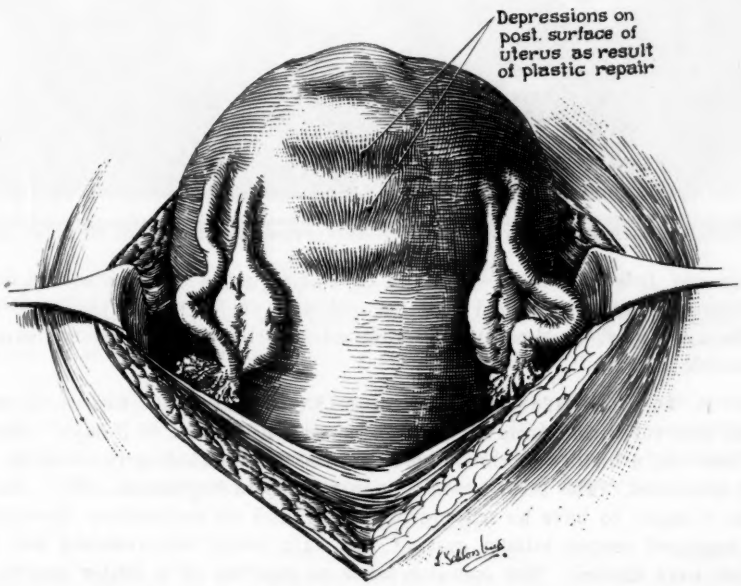

Fig. 12 (Case 2).—Appearance of posterior surface of uterus at cesarean section after delivery of child. Note the indentations from the sutures shown in Fig. 9.

normally on Oct. 5, 1950. On Oct. 21, 1950, the basal temperature chart showed that ovulation had occurred and 12.5 mg. progesterone intramuscularly was started. This was increased to 25 mg. on Nov. 20, 1950.

Chorionic gonadotropin and pregnanediol studies were carried out as follows:

DAY AFTER LAST MENSTRUAL PERIOD	CHORIONIC GONADOTROPIN (INTERNATIONAL UNITS PER LITER BLOOD SERUM)	PREGNANEDIOL (MILLIGRAMS PER 24 HOURS)
33	3,200	5.3
39	30,000	6.8
46	64,400	7.6
53	79,760	8.2
58	45,900	—
67	103,250	15.0
76	60,800	—
93	56,200	9.7
121	8,900	20.6
150	—	28.8
166	2,500	—

The expected date of confinement was July 6, 1951. Activities were limited to eating and toilet privileges. Although by Feb. 1, 1951, there seemed no further indication for therapy, the patient insisted that the progesterone be continued and this was done until the male baby was delivered by cesarean section May 31, 1951. She had fallen into labor prematurely. The child was estimated to weigh 4½ pounds and has since done well.

Fig. 13 (Case 3).—Hysterogram showing widely separated horns of bicornuate uterus.

Summary and Interpretation.—This is a case of repeated abortion with a double uterus but with serious inadequacy of luteal function and with evidence of thyroid and adrenal disturbance. Therapy for these abnormalities resulted in a living child without surgical correction of the double uterus.

CASE 4.—A. D., No. 554288, was born in 1918. The menarche was at 12 years of age. The menstrual interval varied from 30 to 40 days with a duration of 5 days. She was generally well. There was a history of three abortions; the first in 1946 at two months. The specimen was not examined. The second was at two months in September, 1947. In November, 1947, she was thought to have an ectopic pregnancy and an exploratory operation was performed. A ruptured corpus luteum cyst of the right ovary was removed and three small uterine fibroids were excised. The operator made no mention of a double uterus. The third abortion was at 2 to 3 months in April, 1948. No specimen was noted.

Work-up in October, 1948, while she was not pregnant showed an inadequate luteal phase as evidenced by no detectable pregnanediol and a flat basal temperature chart. The patient weighed 185 pounds and had a basal metabolic rate of −5 and cholesterol of 205 mg. per 100 c.c. blood. She was taking 1½ grains thyroid daily.

Therapy consisted of a high-protein, low-caloric diet, thyroid, and supplementary progestogen, 30 mg. of Progesterol daily, during the luteal phase.

In 1949 she weighed 175 pounds and again aborted at 2½ months. The conception was classified as a Carnegie VI. The chorionic gonadotropic and pregnanediol values of this pregnancy were grossly inadequate as follows:

1949 PREGNANCY (FIG. 14)

DAY AFTER LAST MENSTRUAL PERIOD	CHORIONIC GONADOTROPIN (INTERNATIONAL UNITS PER LITER BLOOD SERUM)	PREGNANEDIOL (MILLIGRAMS PER 24 HOURS)
33	0	—
39	800	—
44	2,000	tr.
52	—	2.9
60	7,740	6.0
68	8,500	—
75	37,000	1.8
88	aborted	

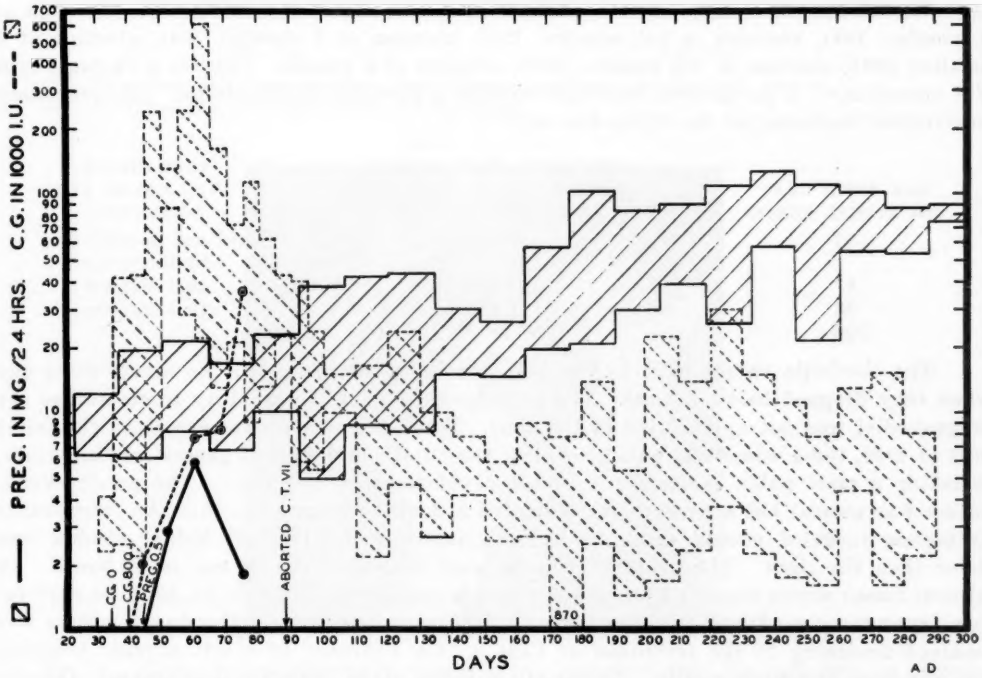

Fig. 14 (Case 4).—Serum chorionic gonadotropin value plotted in dotted line. Urinary pregnanediol excretion value plotted in solid line. The extreme range of chorionic gonadotropin values for 24 normal pregnancies is designated by the interrupted cross-hatched area, and the extreme range of excretory pregnanediol values is designated by the solid cross-hatched area for the same 24 normal pregnancies.

The thyroid, 1½ grains per day, was contined. In 1950 the luteal phase was supplemented with 60 mg. of oral progestogen per day, or 12.5 mg. of progesterone intramuscularly. A fifth pregnancy aborted at 2½ months. The conceptus was classified as a Carnegie VI. The chorionic and pregnanediol studies were somewhat improved as follows:

1950 PREGNANCY

DAY AFTER LAST MENSTRUAL PERIOD	CHORIONIC GONADOTROPIN (INTERNATIONAL UNITS PER LITER BLOOD SERUM)	PREGNANEDIOL (MILLIGRAMS PER 24 HOURS)
34	631	1.9
42	8,700	2.2
49	18,200	5.0
56	30,400	6.0
69	aborted	

On Oct. 21, 1950, and again on Nov. 30, 1951, a hysterogram revealed a double uterus. Because of the abortion of the fifth pregnancy in the face of a much improved chorionic value and the occurrence of two normally developed fetuses, it was decided to repair the double uterus. This was done in July, 1951, by the technique used in Case 2. A postoperative hysterogram in December, 1951, showed a globular cavity. The patient had a normal menstrual period Jan. 1, 1952, and was delivered of a normal male child by section Sept. 9, 1952. An intravenous pyelogram showed two kidneys.

Summary and Interpretation.—This is a case of repeated abortion with evidence of inadequate luteal function. Correction of this defect did not result in a living child. It was therefore concluded that the double uterus was also a factor, and this has now been surgically corrected.

CASE 5.—E. H., No. 388102, was born in 1916 and married July 31, 1937. No contraception has been practiced. Menarche was at age 12. The menstrual interval was 28 days with a duration of 6 days. Soon after marriage in 1937 she developed marked generalized hirsutism, but no menstrual abnormality or other sign of masculinization.

The obstetrical history was as follows: 1939, abortion at 5 months; 1940, abortion at 3 months; 1941, abortion at 3½ months; 1942, abortion at 3 months; 1944, abortion at 3 months; 1946, abortion at 3½ months; 1949, abortion at 3 months. The was a Carnegie type VII conceptus.[9] A postpartum curettage revealed a probable double uterus. This pregnancy was studied beginning at the eighty-first day:

DAY AFTER LAST MENSTRUAL PERIOD	CHORIONIC GONADOTROPIN (INTERNATIONAL UNITS PER LITER BLOOD SERUM)	PREGNANEDIOL (MILLIGRAMS PER 24 HOURS)
81	28,000	could not be read due to impurity
87	23,400	49.3 impure
93	6,516	15.4 impure
100	aborted	

The chorionic values were in the lower limits of normal until the ninety-third day when they dropped below normal. The full significance of the inability to crystallize the pregnanediol was not appreciated at the time. When the patient was examined the latter part of 1950, there was slight enlargement of the clitoris and marked generalized hirsutism, including a male pubic escutcheon. Breast development was normal. The pelvic examination was normal but a hysterogram revealed a double uterus (Fig. 15). An intravenous pyelogram revealed normal excretory tracts bilaterally but the left kidney shadow was lower than the right. The urinary 17-ketosteroid excretion was 60 mg. in 24 hours. An adrenal tumor above the left kidney was strongly suggested. On Feb. 10, 1951, an exploratory laparotomy confirmed the presence of a left suprarenal mass. The double uterus was repaired according to the technique of Case 2. On February 26 a left adrenal adenoma was removed transthoracically. Twenty-four hours after operation the urinary 17-ketosteroid value was 5.5 mg. in 24 hours.

Menses continued normally. The last menstrual period was June 17, 1951. This pregnancy was studied as follows:

DAY AFTER LAST MENSTRUAL PERIOD	CHORIONIC GONADOTROPIN (INTERNATIONAL UNITS PER LITER BLOOD SERUM)	PREGNANEDIOL (MILLIGRAMS PER 24 HOURS)
51	72,000	—
58	129,280	6.2
79	34,000	—
114	—	9.6
127	miscarriage	

Summary and Interpretation.—This disappointing result may have been caused by a rapid fall of chorionic gonadotropin with a slow placental progesterone "take over" period in the presence of a hyperirritable uterus. It might be hoped that, with progesterone therapy, this patient would carry to term.

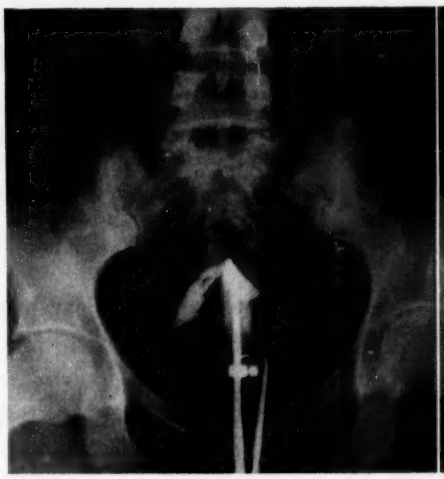

Fig. 15.

Fig. 16.

Fig. 15 (Case 5).—Preoperative hysterogram showing bicornuate uterus.
Fig. 16 (Case 5).—Postoperative hysterogram.

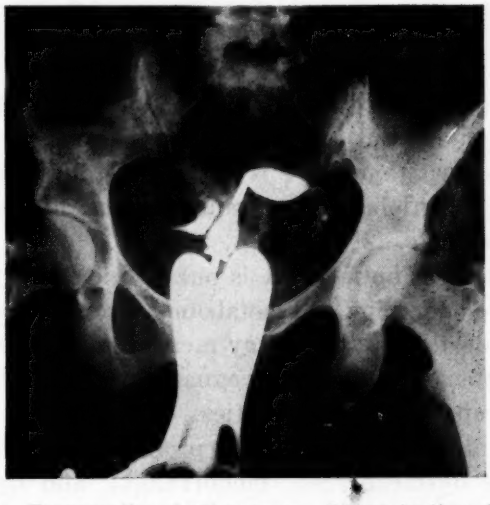

Fig. 17 (Case 6).—Preoperative hysterogram, demonstrating the left side of uterus didelphys. The radiopaque material had previously been injected into the right side and revealed a picture similar to that of the left.

Failure might also have been due to an inadequate excision of the septum although this was not thought to be the case.

CASE 6.—E. McD., No. 444131, was born in 1917, married July 17, 1937. The menarche occurred at 14 years of age and the menstrual interval was 30 days with a duration of 5 days. She had had a miscarriage in 1939 at 5½ months. The baby lived 45 minutes. A second miscarriage in 1946 occurred again at 5½ months with delivery of a normally developed infant. In November, 1947, the patient was admitted to the Johns Hopkins Hospital for study of repeated abortion and secondary infertility. The last menstrual period was Nov. 4, 1947. Pelvic examination revealed a cervix divided by a septum making two separate cervical ora. Two uterine horns were easily palpable. Uterotubal insufflation on the right side was successful with a gas pressure of 150/80. On the left side it was unsuccessful. An endometrial biopsy taken Dec. 1, 1947, disclosed "late interval

(secretory) endometrium (No. 73691).'' An intravenous pyelogram showed no right kidney and a marked hydronephrosis of the left kidney. The patient was discharged without further study or therapy.

The menses were regular until Jan. 15, 1950. At this time a pregnancy in the right side of the double uterus was diagnosed and progressed uneventfully until July 4, 1950, when vaginal bleeding was noted. Spontaneous delivery of a normal dead child took place on July 6, 1950. An autopsy revealed no abnormality and the case was classified as an immature fetal death in utero during labor, the fetus Carnegie VII. Because of the normal development of the fetuses it was thought that the double uterus was an important etiological factor in the abortions.

She was admitted for plastic repair of the uterus. A hysterogram on Sept. 6, 1950, showed a double uterus (Fig. 17) with the left tube dilated and the right patent and delicate.

The operation was carried out Sept. 6, 1950, by Dr. O'Donnell and Dr. Te Linde. The septum was excised from below and a wedge removed from the fundus to excise the septum. The convalescence was uneventful. The patient was the wife of an army officer and was soon transferred from the Baltimore area. There was no opportunity for postoperative studies. Nov. 15, 1951, she reported by mail that she had not become pregnant.

Summary and Interpretation.—This patient had a history of repeated abortion which was thought to be due to the double uterus because of the normal development of the conceptuses. There is also a factor of infertility which has not been completely studied and which has prevented complete evaluation of the success of the plastic procedure.

Comment

As has been implied above, it is unreasonable to expect a plastic repair of a double uterus to be successful in the correction of any gynecological condition unless it has been shown that there is a reasonable etiological association. In Case 1, for example, the etiology was unequivocal and unification offered a happy alternative to hysterectomy.

In repeated abortion, however, it is our opinion that adequate study must eliminate some of the endocrine and metabolic causes of repeated abortion before plastic repair is undertaken. This may mean that a given patient must have the fortitude to attempt repeated pregnancies before being classed in the group with serious reproductive difficulties.

In our opinion it is doubtful if this procedure should be undertaken for such indications as dysmenorrhea, menorrhagia, and dyspareunia, but premature labor and primary sterility may be an indication if persistent and adequate study reveals no other cause.

The surgical procedure used for the unification herein reported differs in an important detail from the Strassmann procedure. In the latter, the uterine incision is transverse from cornu to cornu across the uterine fundus with the final suture line in the anterior-posterior midplane of the uterus. Such a procedure incises rather than excises the septum. The operation herein reported attempts to excise the muscular septum by a triangular incision, resulting in a final vertical midline incision. This has the additional advantage of avoiding injury to the cornua.

Whether these theoretical considerations are of importance remains to be determined, but it was thought that the failure in Case 4 might have been due in part to inadequate excision of the septum.

The association of anomalies of the urinary tract with double uterus has been cited many times. However, very little consideration is given this problem in most obstetrical reviews. Urological investigation was carried out in the six cases reported. There was a congenital absence of one kidney in 3 of these women. Although the present series is small, the frequent association of the two anomalies in single case reports in the literature leads one to suspect that a larger series would reveal a high percentage of such associated anomalies.

Summary

Approximately one of every four women with a double uterus will have some serious reproductive problem and no living children. In women with such reproductive difficulties, namely, premature labor or repeated abortion, surgical unification of the double uterus may be followed by term delivery of a living child, but only when adequate investigation of both husband and wife reveals no other cause for the difficulty. Surgical unification may also be useful in the rare case of unilateral hematometra.

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CUL-DE-SAC ASPIRATION AND OTHER DIAGNOSTIC AIDS FOR ECTOPIC PREGNANCY

A Review of 219 Cases

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PERHAPS the most difficult gynecological lesion to diagnose is unruptured ectopic gestation.[1] There are many factors to consider in making the diagnosis. History and physical findings are important, but some patients are seen with atypical histories and physical findings suggestive of ectopic gestation and one must resort to diagnostic aids to avoid unnecessary surgery. The error in diagnosis given by Torpin[2] is 14.8 per cent to 49 per cent.

Rather than review the history and physical findings, as has been done by many authors[3, 4, 5] in the past, we have attempted to review the diagnostic aids used in making a positive diagnosis of ectopic pregnancy or in ruling out the presence of this condition in suspected cases.

Material

One hundred cases of proved ectopic pregnancy treated in this hospital from January, 1943, to March, 1952, were reviewed. In addition, there were 119 cases admitted during the years 1949 through 1951 where ectopic pregnancy was suspected but was not present. All of these 119 patients had examination under anesthesia and cul-de-sac aspiration performed in order to rule out eccyesis. This procedure has been in use in this hospital for over twenty years.

Diagnostic Aids

I. Biological Pregnancy Tests.—

We do not feel that the biological pregnancy tests are of value in many cases because intrauterine pregnancy is frequently considered in the differential diagnosis. The time required for performing the test is obviously a disadvantage in acute cases. As shown in Table I, the pregnancy tests were positive in only 7 (38 per cent) of 18 cases of ectopic pregnancy where it was performed.

Table I shows the results of the pregnancy tests in 18 cases of proved ectopic pregnancy where performed. It is generally accepted that in intrauterine pregnancy, the pregnancy test may remain positive for 10 to 14 days after fetal death. In our series all of the positive pregnancy tests occurred when less than 19 days of vaginal bleeding had taken place. Where vaginal bleeding had been present for a longer period of time, all of the tests were negative. Thus we may infer that the biological pregnancy tests are of value in ectopic pregnancy only if vaginal bleeding has been present for less than approximately three weeks.

TABLE I. RESULTS OF BIOLOGICAL PREGNANCY TESTS IN ECTOPIC PREGNANCY

NO. OF DAYS OF VAGINAL BLEEDING	RESULT OF PREGNANCY TEST
0	Pos.
0	Pos.
4	Rat died
4	Pos.
5	Rat died
7	Neg.
7	Pos.
7	Pos.
14	Neg.
15	Pos.
17	Rat died
19	Pos.
28	Neg.
30	Neg.
30	Neg.
45	Neg.
90	Neg.
180	Neg.
Total: 18 Cases	
7 Positive (38%)	
8 Negative	
3 Rat died	

Whether the ectopic pregnancy was intact or ruptured did not affect the results of the pregnancy tests. Positive and negative tests were about evenly distributed in both the ruptured and unruptured groups.

II. Dilatation and Curettage.—

Dilatation and curettage were performed in 15 cases of proved ectopic pregnancy. In addition there were 4 cases where tissue was passed through the cervical os; thus, we had tissue available for microscopic examination in 19 cases. The pathologic findings in these 19 cases are listed in Table II.

TABLE II. CORRELATION OF DURATION OF BLEEDING AND ENDOMETRIAL FINDINGS IN ECTOPIC PREGNANCY

NO. OF DAYS OF VAGINAL BLEEDING	MICROSCOPIC FINDINGS OF ENDOMETRIUM
0	Secretory endometrium, no decidua
1	*Decidua, no villi
4	Proliferative endometrium
5	*Decidua, no villi
5	Proliferative endometrium
9	*Decidua, no villi
10	Decidua, no villi
14	Proliferative endometrium
15	Decidua, no villi
21	Decidua, no villi
24	Proliferative endometrium
28	*Autolytic tissue
30	Proliferative endometrium
30	Proliferative endometrium
45	Proliferative endometrium
60	Proliferative endometrium
60	Proliferative endometrium
90	Proliferative endometrium
Unknown	Decidua, no villi
Total: 19 Cases	
7 Decidual reaction, no villi present	
10 Proliferative endometrium	
1 Secretory endometrium	
1 Autolytic tissue	

*Tissue obtained which was passed spontaneously through the cervical os. In all other cases, dilatation and curettage were performed.

We consider the presence of decidual reaction without the presence of villi as indicating ectopic gestation. Again, here, if intrauterine pregnancy is present, dilatation and curettage are not advisable. The time element required for preparing microscopic sections is also a disadvantage in acute cases.

Bleeding which takes place in ectopic pregnancy is of uterine origin.[6] The patient may pass a complete decidual cast or the decidua may be expelled in small fragments over a period of time.[7] Table II shows the microscopic findings of the endometrium correlated with the number of days of vaginal bleeding.

We have felt in the past that the decidua is completely passed within 10 to 14 days[8] so that dilatation and curettage after that time do not aid in the diagnosis; however, in our series decidual reaction without villi was seen as late as 21 days after onset of vaginal bleeding. Thus, the decidua may not be entirely expelled for a period of 3 weeks.

III. Pelvic Examination Under Anesthesia.—

When any patient is admitted with a diagnosis of possible ectopic pregnancy, she is scheduled for a pelvic examination under anesthesia and cul-de-sac aspiration. These procedures are omitted in patients in shock when the diagnosis is obvious and the delay is unwarranted.

In 100 cases of proved ectopic pregnancy, examination under anesthesia was performed in 69 instances. Adnexal masses were palpable in 63 cases and cul-de-sac masses in 12 cases. These are shown in Table III.

In many instances pelvic masses were not felt during pelvic examination with the patient conscious but were easily palpated with her under anesthesia.

TABLE III. ONE HUNDRED CASES ECTOPIC PREGNANCY—69 EXAMINED UNDER ANESTHESIA

Adnexal mass palpable	63 Cases
Unilateral 60	
Bilateral 3	
Cul-de-sac mass palpable	12 Cases

IV. Cul-de-Sac Aspiration.—

We feel that the most important single diagnostic aid, where ectopic pregnancy is suspected, is needle aspiration of the posterior cul-de-sac. The procedure is simple and can be carried out in the hospital or in the clinic. Usually it is done in the operating room simultaneously with examination under anesthesia. It may be performed in the office or clinic with no more pain than ordinary venipuncture if the patient is cooperative.

The cul-de-sac is entered in the midline, using a long 15 to 18 gauge needle attached to a 10 or 20 c.c. syringe so that tiny clots can be aspirated. Old blood is usually obtained where ectopic pregnancy is present. This old blood has a brownish hue when spread on a white compress. In acute ectopic pregnancy with much fresh bleeding the blood does not show the characteristic brownish hue.

In the 100 cases of proved ectopic pregnancy, the preoperative diagnosis before the abdomen was entered was correct in 92 per cent of the cases. There were 8 errors in diagnosis. These are listed in Table IV, showing that examination under anesthesia was done in only half the cases and cul-de-sac aspiration was not performed in any case.

In the 119 patients not having ectopic pregnancy but in whom it was suspected, examination under anesthesia and cul-de-sac aspiration were performed in all instances. We have adequate proof that these patients did not

have ectopic pregnancy in that some of them were operated upon for other conditions and the rest were adequately followed in the clinic for a sufficient period of time to exclude the possibility of the diagnosis having been missed.

TABLE IV. EIGHT ERRORS IN PREOPERATIVE DIAGNOSIS IN 100 CONSECUTIVE ECTOPIC PREGNANCIES

ERRONEOUS PREOPERATIVE DIAGNOSIS	EXAMINATION UNDER ANESTHESIA	CUL-DE-SAC ASPIRATION
1. Chronic salpingitis	Yes	No
2. Ovarian cyst	Yes	No
3. Ovarian cyst	Yes	No
4. Chronic salpingitis	Yes	No
5. Not operated upon. Died	No	No
6. Appendicitis	No	No
7. Appendicitis	No	No
8. Fibroid	No	No

There were 10 patients (Table V) in the group in which laparotomy was performed with an erroneous preoperative diagnosis of ectopic pregnancy. In 7 of these 10 cases, laparotomy was deemed necessary due to other pathology found. However, in 3 of the 10 it was felt that the laparotomy was unnecessary. In 42 of the 119 cases, following examination under anesthesia and cul-de-sac aspiration, it was felt that other pathology was present and laparotomy was performed at that time or at a later date. These laparotomies were deemed necessary by the other pathology found.

It is extremely important that one correlate the history, physical findings, and the result of the cul-de-sac aspiration to arrive at a correct diagnosis. Each case must be individualized and the cul-de-sac aspiration must be considered as a diagnostic aid along with the rest of the findings. There were a total of 197 aspirations performed in both groups (that is, 119 suspected ectopic pregnancies and 100 proved ectopic pregnancies). Table V shows that there were in this group 10 (5.1 per cent) false positive and 1 (0.5 per cent) false negative results.

In those instances where cul-de-sac aspiration was positive, the percentage of correct diagnosis was 89.7 per cent (Table V). Where cul-de-sac aspiration was negative, the percentage of correct diagnosis was 100 per cent, but where no cul-de-sac aspiration was performed this fell to 63.6 per cent.

TABLE V. CORRECT PREOPERATIVE DIAGNOSIS BASED ON CUL-DE-SAC ASPIRATION

	NO. OF PATIENTS	NO. CORRECT DIAGNOSES	NO. INCORRECT DIAGNOSES	% CORRECT DIAGNOSIS
Cul-de-sac aspiration, positive	87	77	10	89.7%
Cul-de-sac aspiration negative	110	110	0	100.0%
No cul-de-sac aspiration	22	14	8	63.6%
Total	219	201	18	91.8%
197 Cul-de-sac aspirations		10 False positive (5.1%)		
		1 False negative (0.5%)		

Evaluation of Aspirated Fluid

As a general rule we have been able to classify the type of fluid aspirated through the cul-de-sac with various diagnoses as follows:

A. Clear serous straw-colored fluid—normal, negative pelvis.
B. Turbid serous fluid—pelvic inflammatory disease.

C. Blood-tinged serous fluid—ruptured ovarian cysts, ovulation bleeding, occasionally pelvic inflammatory disease.

D. Bright red, grossly bloody fluid—recent bleeding, corpus luteum cyst with much bleeding, recently ruptured ectopic pregnancy with fresh bleeding, traumatic cul-de-sac aspiration.

E. Old blood, brownish-colored fluid—ectopic pregnancy with intraperitoneal bleeding over few days or weeks.

F. No return—equivocal, tap should be repeated.

Diagnoses Confused With Ectopic Pregnancy

In the 119 cases where ectopic pregnancy was suspected but was not found, it was interesting to note what the true diagnosis was. These patients were either operated upon for other pathology or were followed in the clinic for several months to exclude the possibility of an ectopic gestation having been missed. Table VI shows that intrauterine pregnancy was present 39 times. Next came 33 cases of pelvic inflammatory disease. Endocrinopathies such as functional bleeding, endometrial hyperplasia, and polycystic ovaries were seen in 23 cases. In 10 instances the final diagnosis was negative pelvis since we were unable to find any definite pelvic disease. Other diseases less frequently confused with ectopic pregnancy were ovarian cyst, 9 cases; fibroid uterus, 3 cases; acute appendicitis, 1 case; and postoperative adhesions, 1 case. Thus it can be seen that intrauterine pregnancy and pelvic inflammatory disease account for about 50 per cent of the cases mimicking ectopic pregnancy.

TABLE VI. FINAL DIAGNOSIS IN 119 CASES OF SUSPECTED ECTOPIC PREGNANCY RECEIVING EXAMINATION UNDER ANESTHESIA AND CUL-DE-SAC ASPIRATION

Intrauterine pregnancy: threatened abortion, incomplete abortion, tender corpus luteum cyst	39 cases
Pelvic inflammatory disease	33 cases
Endocrinopathies: functional uterine bleeding, endometrial hyperplasia, polycystic ovaries	23 cases
Negative pelvis	10 cases
Ovarian cyst	9 cases
Fibroid uterus	3 cases
Acute appendicitis	1 case
Postoperative adhesions	1 case
Total	119 cases

Complications of Cul-de-Sac Aspiration

In the total of 197 patients having cul-de-sac aspiration, there were two instances of accidental perforation of the bowel. In both cases feces were returned on aspiration in patients who did not have ectopic pregnancies. These patients had smooth afebrile courses with no untoward effects. We do not feel that there are any valid contraindications to cul-de-sac aspiration other than shock in an acute case where delay is unwarranted.

Summary and Conclusion

1. One hundred cases of proved ectopic pregnancy and 119 cases of suspected ectopic pregnancy have been analyzed to determine the value of various diagnostic aids.

2. Cul-de-sac aspiration was performed in 197 cases. There were 10 false positive (5.1 per cent) and 1 false negative (0.5 per cent) results.

3. The correct preoperative diagnosis was made in 92 per cent of the 100 cases of ectopic pregnancy. In all 8 cases where the preoperative diagnosis was not correct, cul-de-sac aspiration was not performed.

4. Intrauterine pregnancy and pelvic inflammatory disease are the conditions most often misdiagnosed as ectopic pregnancy.

5. In 197 cases of cul-de-sac aspiration, there were 2 instances where the bowel was accidentally entered. There was no untoward effect following this.

6. Pelvic examination under anesthesia is of definite value to aid in making a diagnosis. Frequently adnexal and cul-de-sac masses and enlarged pregnant uteri are palpable under anesthesia which were not felt with the patient conscious.

7. Endometrial tissue was examined in 19 cases of ectopic pregnancy. Decidua without villi was present in 7 cases. If vaginal bleeding had been present over 21 days, no decidua was found and the endometrium was in the proliferative phase.

8. The biologic pregnancy tests were done in 18 cases of ectopic pregnancy. They were positive in 7 (38 per cent) of the cases. The pregnancy test was not positive in any case where vaginal bleeding had been present over 19 days.

9. Of 119 cases of suspected ectopic pregnancy unnecessary laparotomy was done in only 3 cases. This low incidence is attributed to the procedure outlined.

10. History and physical findings alone are not sufficient in many instances to diagnose or exclude ectopic pregnancy. We find that cul-de-sac aspiration and examination under anesthesia are the most important diagnostic aids. They are simple and of negligible risk to the patient.

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277 LINWOOD AVENUE

THE CORPUS SPONGEOSUM OF THE URETHRA: ITS POSSIBLE ROLE IN URINARY CONTROL AND STRESS INCONTINENCE IN WOMEN

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IT HAS become apparent in recent years that urinary control in women cannot be explained simply on the basis of a sphincter mechanism. Recognition of this fact has inspired numerous cystometric and roentgenographic investigations, in addition to the continued study by detailed dissection of the musculofascial investments of the urethra. The same techniques have been used also to demonstrate the mechanism of "stress" (orthostatic) incontinence.

Our knowledge of both these related subjects has been increased considerably by such studies. Yet the physiological mechanism of urinary control in the female has remained obscure. The report[1] of the round-table discussion in London, in 1950, states: "it was agreed that the exact mechanism of stress incontinence is not completely known."

The most important elements in urinary control are, without doubt, the musculofascial sphincters. Kelly[2] recognized a single sphincter, situated at the bladder neck (Fig. 1, *a*). Martius[3] described two sphincters: one voluntary, composed of striated muscle (rhabdosphincter), the other involuntary (the lissosphincter). These are said to resemble crossed horseshoes, enclosing the urethra (Fig. 1, *b*). Kennedy[4] found three distinct sphincters, corresponding fairly well to the sphincter mechanisms demonstrated by Curtis, Anson, and Ashley.[5] These are: (1) "the internal, involuntary sphincter" situated at the bladder neck; (2) "the true sphincter" which surrounds the middle and posterior thirds of the urethra; and (3) "the external, accessory, voluntary sphincter," composed of the bulbocavernosus muscles, which compress laterally the outer third of the female urethra (Fig. 1, *c*). J. W. Davies[6] and Reich and associates[7] name four urethral sphincters (Fig. 1, *d*).

Coincident with the search for more detailed understanding of the sphincter mechanism, x-ray studies of micturition in normal and incontinent women have shown that other factors are involved. These include the position of the urethra, its length, width, and tonicity. The oblique course of the urethra into the bladder has been emphasized. E. Held[8] notes that "increased bladder filling causes the urethra to have a more tangential course to the floor of the bladder." Thomsen's[9] investigations indicate that the intrinsic muscles of the urethra itself are largely responsible for its form and tension.

Conversely, impairment of the musculofascial sphincters, by obstetrical trauma primarily, is indisputably the principal cause of "stress" incontinence. In addition (or as a result), cystourethrography and fluoroscopic studies reveal loss of urethral tonicity, with shortening and widening of the urethra.

The "funnel effect" at the vesicourethral junction, originally demonstrated by Rubin and his associates,[10] has been amply confirmed. Decrease in the length of the urethra, from the normal 4 to 4.5 cm. to approximately half this length (Frost[11]), produces the "accordion effect" graphically illustrated by Ball, Douglas, and Fulkerson.[12] Descent of the widened bladder neck (Muellner,[13] Millin and Read[14]) is responsible for the apparent "herniation" of this portion of the urethra through the weakened subjacent musculofascial supports, described by Ingelman-Sundberg.[15]

Investigations of this type and purport have been numerous and are remarkable for their ingenuity, variety, and general excellence. Further work

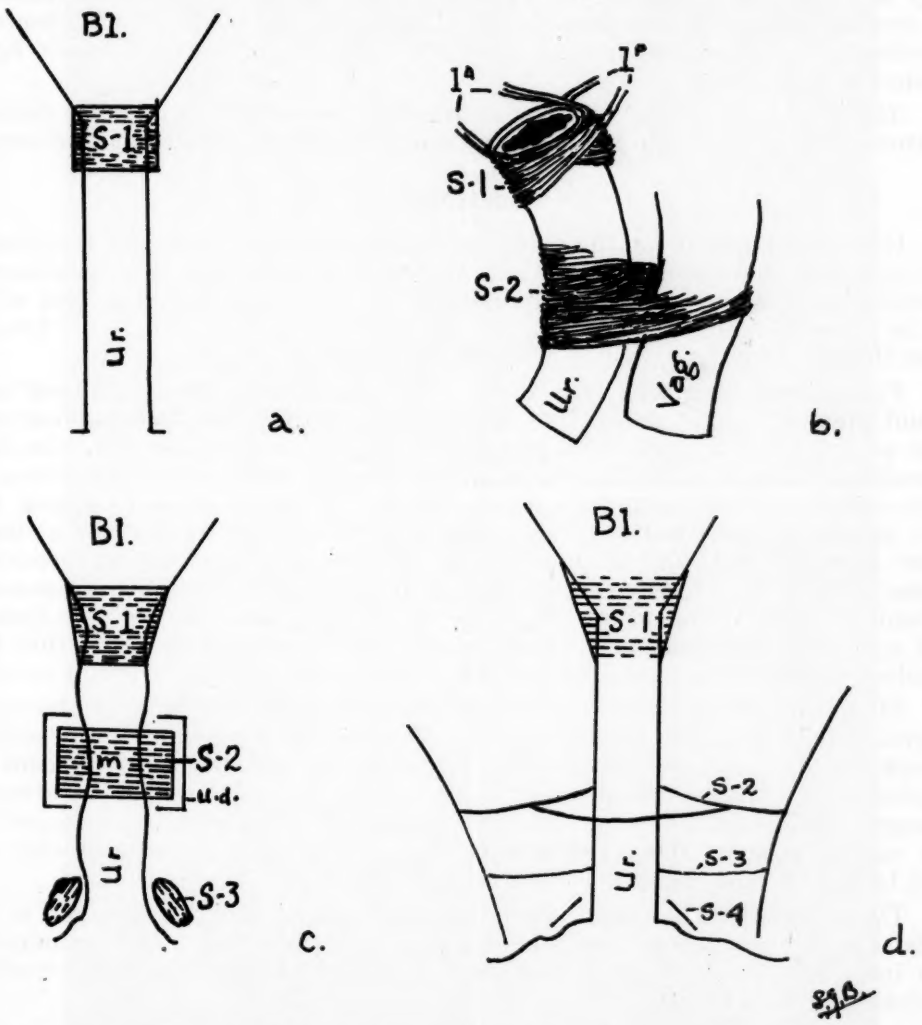

Fig. 1.—Sphincters of the female urethra, diagrammatic presentation illustrating: *a*, a single sphincter (*S-1*) at the bladder neck (Kelly); *b*, two sphincters: an involuntary lissosphincter (*S-1*) at the bladder neck, with one loop (*1ª*) drawing anteriorly and another (*1ᵖ*) drawing posteriorly, and (*S-2*) a voluntary, striated rhabdosphincter (Martius); *c*, three sphincters: an involuntary levator sphincter at the bladder neck (*S-1*); the constrictor urethrae membranaceae *m*, called "the true sphincter," enclosed in the urogenital diaphragm (*u.d.*), and the bulbocavernosus muscles (*S-3*), which are "the external, accessory, voluntary sphincter" (Kennedy); and *d*, four sphincters: an involuntary sphincter at the bladder neck (*S-1*), decussating fibers of the levator ani (*S-2*), a voluntary sphincter of the membranous urethra (*S-3*), and the tendon connecting the anterior ends of the bulbocavernosus muscles (*S-4*) (Davies).

along these lines may add to or clarify our knowledge of the elements already cited, but it is unlikely that more sphincters or further cystometric and roentgenographic studies will reveal an unknown factor in the mechanism of urinary control and/or stress incontinence. It is more probable that the unknown factor, the missing piece of the puzzle, is one which has not been considered in this respect.

It is the thesis of this article that the overlooked element in urinary control is the rich venous network which lies between the urethral mucosa and its musculature. This has been called[16] a "cavernous vascular submucosa, the erectile tissue, or corpus spongeosum of the urethra." Its function, we believe, may be compared to that of the "washer" which keeps a faucet from leaking. In conjunction with the musculofascial sphincters and the other elements previously described, the spongy, erectile "washer" is essential for *watertight* closure of the bladder.

The presence of these vascular channels in the urethra is noted in various anatomic and gynecologic publications, and is described in Piersol's *Anatomy*.[17]

Material

Our own material for the study of urethral sinuses consists of 6 urethras and adjacent portions of the trigones, all removed from fresh female cadavers. Sections were taken, under the direction of Dr. Alexander Kushner, just within the external meatus (Fig. 2, *a*), 1.5 cm. from the meatus (Fig. 2, *b*), 3.0 cm. from the meatus (Fig. 2, *c*), and at the bladder neck (Fig. 2, *d*).

From these specimens it is evident that numerous venous channels surround the urethra for almost its entire length. Only at the bladder neck and just within the mucocutaneous junction at the external os are the veins less abundant. This is particularly true at the bladder neck, where the stroma is more dense and the veins have thicker walls. Between these extremes, the rich plexus of veins is remarkably thin walled. In many instances a single layer of wavy, convoluted endothelium encloses a number of erythrocytes. These veins lie in a loose areolar stroma. It is apparent that such sinuses are capable of marked distention. Therefore their designation as "erectile tissue" and a "corpus spongeosum" is fully warranted. It should be noted that the number of sinuses is excessive for the ordinary demands of a blood supply.

Stress incontinence of urine not infrequently develops or becomes aggravated in postmenopausal women. This has been attributed to "senile" atrophy of the periurethral muscles, including the sphincters. By means of vaginal smears, Salmon, Walter and Geist[18] demonstrated the value of estrogen therapy. Re-establishment of urinary control coincides with improvement in the vaginal smear. When estrogen is discontinued such patients quickly return to their former degree of stress incontinence.

These therapeutic results seem too pronounced and too prompt to be metabolic effects of estrogen on long-damaged and attenuated muscle sphincters. Our interpretation of these phenomena, based on the hypothesis of "the washer mechanism," is as follows:

1. Impairment of urinary control, originally produced by obstetrical trauma to the paraurethral musculofascial supports (including the sphincters), is aggravated by postmenopausal diminution of blood flow in the venous plexus of the urethral submucosa. This added factor may "tip the balance" toward manifest loss of control, or to a higher degree of stress incontinence.

2. Estrogens increase pelvic vascularity. The venous channels in the urethral submucosa are distended and become turgid. This specific hormonal

effect is more certain and would be more rapid than the alleged anabolic influence of the steroid.

The erectile nature of the venous plexus in the female urethra suggests an analogy to the corpora cavernosa which surround the male urethra. In the

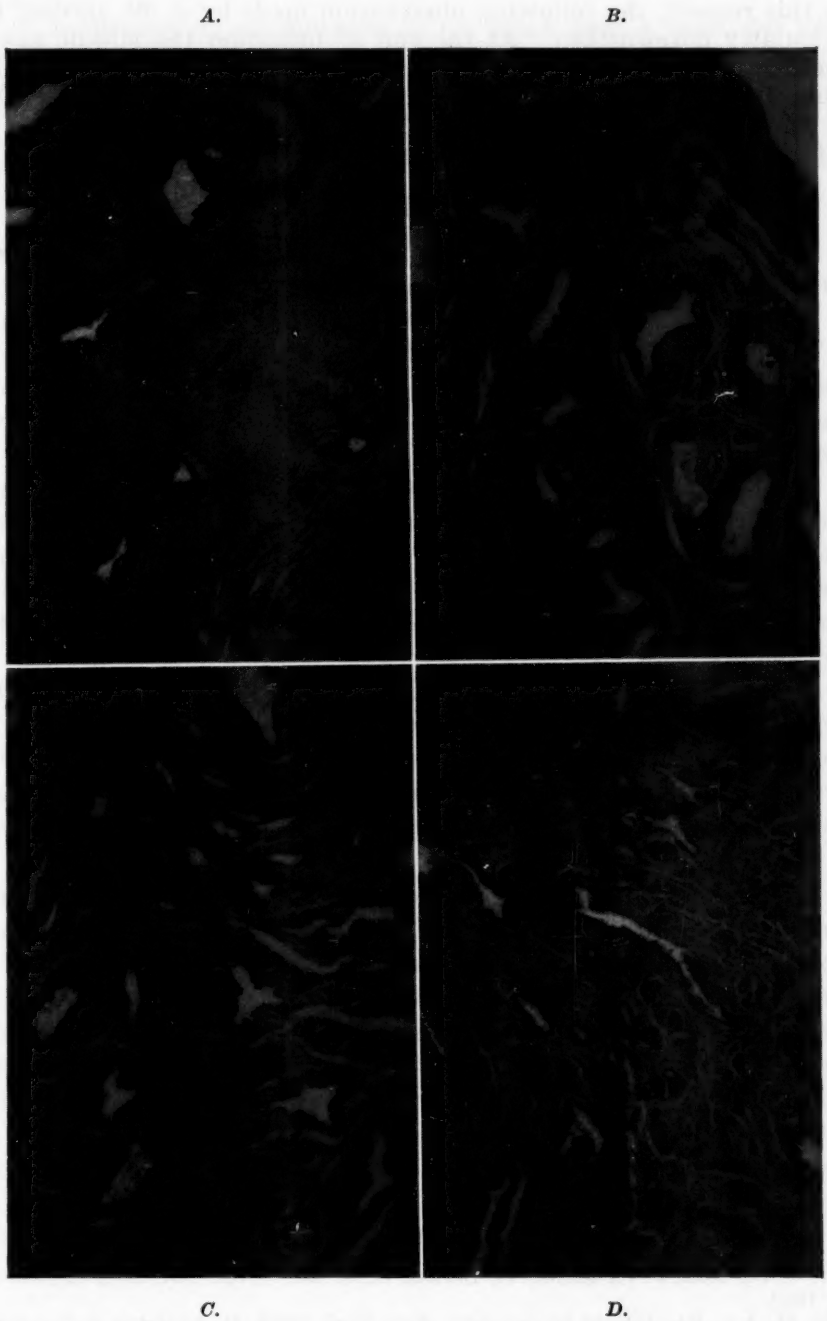

Fig. 2.—Vascular channels in submucosa of female urethra. Photomicrographs of sections: *A*, just within the external meatus, *B*, 1.5 cm. from the meatus, *C*, 3.0 cm. from the meatus, and *D*, at the bladder neck. Clearly evident in *B* and *C* is the rich network of thin-walled veins which constitute "the erectile tissue or corpus spongeosum of the urethra."

male, unrelieved bladder distention produces engorgement of these vascular channels, with consequent partial erection of the penis. In such circumstances, considerable effort, or "stress," may be required to initiate the flow. To a lesser degree "the corpus spongeosum" of the female urethra may exert a similar restraint.

In this respect, the following observation made by J. W. Davies[6] in 1942 is particularly noteworthy: "At the end of urination the middle aged male may become conscious of a slight amount of urinary dribbling. This very annoying disturbance is due to the relaxation of a voluntary muscle which no longer efficiently compresses the bulb of the urethra, and hence permits a small amount of urine to remain unextruded in the penile portion."

Summary and Conclusions

1. There is an unknown factor in urinary control in the female, and the mechanism of stress incontinence is not completely understood.

2. A rich venous plexus lies between the urethral mucosa and its musculature. The venous channels surround the urethra for its entire length. These veins are markedly distensible and form a corpus spongeosum composed of erectile tissue. The number of these venous sinuses exceeds the requirements of a blood supply for the urethra.

3. The hypothesis is advanced that the corpus spongeosum of the urethra acts similarly to a "washer" in a faucet, to complete bladder closure and keep it watertight. It is nevertheless stipulated that the musculofascial sphincters are the most important elements in urinary control, and that complete continence of urine requires approximately normal position, length, width, and shape of the urethra.

4. Incontinence may be produced, or stress incontinence may become aggravated, in postmenopausal women who have suffered antecedent injury to other elements of the control mechanism, through decreased turgidity of the corpus spongeosum. The prompt effectiveness of estrogens in the relief of postmenopausally developed stress incontinence is cited as evidence in favor of this hypothesis.

5. Urinary restraint in the male by engorgement of vascular channels of the corpora cavernosa is offered as evidence that compression of the urethra by expansile (erectile) vascular sinuses may be an effective element of involuntary bladder closure.

Aside from confirmation of the existence of such venous channels in the urethral submucosa, and of their extent and form, these observations are hypothetical and unsupported by direct experimental evidence. They are submitted on that basis, for critical appraisal as an added element in the mechanism of urinary control in the female, and of stress incontinence of urine.

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280 Hobart Street

THE INCIDENCE OF LACTOBACILLUS BIFIDUS IN VAGINAL SECRETIONS OF PREGNANT AND NONPREGNANT WOMEN*

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LACTOBACILLUS bifidus is a gram-positive, nonmotile, nonsporing, microaerophilic bacillus which is frequently branched at one or both ends. Although it has been considered a Corynebacterium or an Actinomyces, the organism is usually classified as a Lactobacillus. As originally reported by Tissier[18] in 1899, *L. bifidus* is unique in that it comprises more than 90 per cent of the bacteria in the stool of the infant who is exclusively breast fed. When the infant is formula fed with cow's milk, the organisms number only 30 to 40 per cent of the flora. As adult foods are added to the diet, the numbers continue to decrease until in older children and adults *L. bifidus* if present at all is found in only small numbers in the stool. The preponderance of *L. bifidus* in the stools of normal breast-fed infants has suggested repeatedly that the organism may have a beneficial effect upon the nutritional state of the infant. Very little is known about the microbiology of *L. bifidus,* however, since it is difficult to culture in the laboratory. Until the work of Torrey,[19] Blaurock[2, 3] and Boventer,[4] attempts to maintain *L. bifidus* in the bifid phase in culture media were largely unsuccessful since this organism is prone to change, presumably by mutation, to an unbranched aerobic rod that differs in other characteristics from the bifid organism. Although these media which are basically infusions of liver with added cystine represent a distinct advance in the primary isolation of the organism, it has not been possible in our laboratory to keep the organisms alive in the bifid phase on repeated subculture in these media. Since the casein-peptone, yeast-autolysate media of Orla-Jensen[11, 12] and Olsen[10] have not been employed by us, we are not in a position to evaluate their reliability. However, with a Teply and Elvehjem[17] medium as modified by Norris, Flanders, Tomarelli, and György,[9] strains have been maintained in the bifid phase for more than three years in our laboratory. Since this medium is chemically defined except for casein hydrolysate and since an even less complex medium without casein hydrolysate has been found by Hassinen, Durbin, Tomarelli, and Bernhart,[7] to support the growth of some strains of *L. bifidus,* means now appear to be available for a more detailed study of the organism. At present, however, it is not known why breast milk promotes the growth of *L. bifidus* in the intestine of the child.

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Since *L. bifidus* regularly makes its appearance in the stool within 48 hours after feeding is begun and reaches maximum proportions within 4 or 5 days after birth, the source of the organism which so quickly populates the colon is a matter of interest. As previously stated, the occurrence of *L. bifidus* in the stools of adults makes fecal contamination a possible source either directly at the time of delivery or indirectly from other parts of the mother's body after birth. There is also the possibility that *L. bifidus* may be present in the vagina which may be the source of the organisms acquired during birth. Weinstein[20] found that the incidence of Döderlein's bacillus, generally regarded as being *L. acidophilus,* was greater in the vaginas of pregnant women and that the incidence increased during pregnancy and reached a peak during the last two months. He did not report the presence of *L. bifidus* but the media employed are now known to be far from optimal for culturing the organism. With liver infusion medium, Blaurock[3] isolated *L. bifidus* from the vaginas of 154 out of 160 pregnant women. Roufogalis[13, 14, 15] and Montagna and Cataldi[8] likewise were successful in obtaining the organisms from this source but did not report such a high incidence. Stolte[16] doubted whether the infant acquired the organism by swallowing, since she could not demonstrate the presence of *L. bifidus* in the mouths of newborn infants nor in the milk or about the breasts of the mothers. She surmised that the portal of entry is the anus. Subsequently, however, Cataldi and Müller[5] expressed the view that colostrum and the skin of the breast were probable sources of *L. bifidus,* particularly for infants born by cesarean section, since they reported the recovery of the organisms from colostrum in 22 per cent of the cases. *L. bifidus* was also recovered in 14 per cent of cases from the skin of the maternal breast immediately after delivery.

Since the modified Teply and Elvehjem medium appears to be superior to media previously employed in studies of the vaginal flora in which the results are not wholly in agreement,[9] it seemed desirable to reinvestigate the incidence of *L. bifidus* in the vaginas of normal women and in women at various stages in pregnancy. It was also hoped to learn whether strains isolated during pregnancy might correspond in cultural and antigenic characteristics with laboratory strains originally isolated from the stools of breast-fed infants.

Methods and Materials

One hundred one vaginal cultures were obtained from 81 different women who were pregnant. In each case, duration of pregnancy was estimated to the nearest calendar month by counting back from the expected date of delivery. No cultures were obtained from the first trimester. The age extremes of this group were 16 and 45 years. Both the median and average ages were 26 years. Twenty-five nonpregnant women who attended a cancer survey clinic served as a control group. A single culture was obtained from each. The age range was 31 to 72 years with a median of 45 years and an average of 46 years. Although it would have been preferable, it was not feasible to obtain a control group among younger nonpregnant women. In addition to the above studies attempts were made to isolate *L. bifidus* from the vaginas and rectums of 3 mothers during labor and again within 5 days after delivery. The stools of their respective infants were likewise cultured for *L. bifidus.*

A clean, boiled but not sterile speculum was inserted into the vagina either without lubricant or with a small amount of lubricant kept away from the edges of the blades. Secretions were collected by swabbing from the posterior fornix and were inoculated at once in broth and agar plates of the modified Teply and Elvehjem medium, hereinafter called "bifid medium." Rectal cultures were also obtained by swabs. The composition of the bifid medium differed from that given previously[9] in that lactose which was previously substituted for glucose was reduced from 140 Gm. to 70 Gm. per liter of double-strength medium and in that vitamin B_{12} and pancreatin were omitted. Ascorbic acid was sterilized by Seitz filtration and was added aseptically to the previously autoclaved medium. The final pH was between 6.5 and 6.6. After the results of the first 50 cultures from pregnant women were recorded, it was learned from evidence which will be presented elsewhere by György, Norris, and Rose[6] that some strains of *L. bifidus* will grow but poorly on this medium unless breast milk is added as a supplement. Accordingly, the remaining specimens from the pregnant group and all of those from the nonpregnant women were cultured on the bifid medium both with and without the addition of breast milk in 2 per cent concentration. Milk added aseptically for this purpose was first skimmed and then sterilized with ethylene oxide according to the method of Wilson and Bruno.[22] Cultures were incubated at 37° C. for 48 hours in an anaerobic atmosphere to which 10 per cent carbon dioxide was added as previously described.[9] On agar plates, organisms were identified by the typical appearance of the colonies and the characteristic morphology of the bacteria in Gram-stained films. Broth cultures were subcultured on agar plates. Cultures were considered positive if *L. bifidus* was isolated on the original agar plates, or in broth tubes, or in both.

Agglutination tests were carried out on 19 strains by a technique which will be given in another report by Williams, Norris, and György.[21]

Results

When *L. bifidus* was isolated, numerous colonies were usually present on the agar plates and bifid organisms were also observed in the liquid cultures. In several instances, however, the organisms occurred originally only in broth tubes. In the case of several strains, also, a change in character from branched organisms to straight rods which grew aerobically and which produced molecular gas occurred after one or more subcultures. The number of positive cultures is recorded in Table I and conveniently classified into 4 groups: (1) controls, consisting of the nonpregnant women; (2) second trimester of pregnancy; (3) third trimester of pregnancy; and (4) at term or overdue. The statistical Chi-square test for one degree of freedom* demonstrates no significant increase in incidence between groups 1 and 2. Since these groups are so similar in numbers and incidence, it was felt permissible to group them together to yield a normal control sample which compares more favorably in numbers with group 3. When compared in this fashion, group 3 shows a tendency to an increased incidence over groups 1 and 2 combined, but this increase is not significant since $X^2 = 2.24$. On the other hand, when groups 1 and 2 combined are compared with group 4, the result is highly significant since $X^2 = 9.27$. Also when group 3 is compared with group 4 the result is likewise highly significant since $X^2 = 6.02$.

In the 51 cultures from the pregnant group and the entire control group in which media both with and without the supplement of breast milk were used, *L. bifidus* when present was usually isolated in both media. There were 20 positive cultures in the pregnant group in 4 of which *L. bifidus* was isolated only in the media without milk and in 3 only in the media with added milk. In

*Computed for us by the late Dr. J. Harold Austin

13, the organisms were present in both media. Likewise in the case of the 5 positive cultures in the control group, *L. bifidus* was obtained simultaneously in both media in 3 cases and in media with and without milk in single instances. The 4 cultures isolated only on media supplemented with breast milk were tested again following isolation and were found to require the presence of breast milk.

Of 28 strains of bifid organisms tested for ability to grow aerobically on agar plates, 26 did not grow and 2 grew poorly. As in a previous report,[9] growth of all strains occurred in liquid medium, probably because of a favorable oxidation-reduction potential in the depths of the tubes. None produced molecular gas. When tested in the simplified medium of Hassinen and co-workers,[7] none of the 19 strains grew; also only 3 of these strains (410, 419, 422) were agglutinated by any of the antisera prepared by Williams and associates.[21]

The attempt to isolate and compare strains of *L. bifidus* from the vaginas and rectums of 3 mothers with strains from the stools of their infants was only partially successful. Bifid organisms were not isolated in pure culture from the vaginas of any mother during labor. Postpartum vaginal cultures were not attempted. In 2 mothers, *L. bifidus* was isolated from the rectum during labor and in all 3 from the rectum post partum. *L. bifidus* was isolated from the stools of only 2 infants. In Table II, it is seen that the rectal strains cultured from Thomas during and following labor do not correspond serologically with each other. Although the rectal strains of Jourdan obtained during and after labor appear to correspond to each other, they differ serologically from both of her infant's strains which in turn differ from each other. Likewise, the strain from Baby Bell is not like that of the mother post partum. The evidence, so far as it goes, therefore, does not indicate the source of *L. bifidus* which is found in the stools of the infant.

TABLE I. INCIDENCE OF L. BIFIDUS IN VAGINAS OF PREGNANT AND NONPREGNANT WOMEN

SOURCE OF CULTURES	NUMBER OF CASES	NUMBER POSITIVE	PER CENT POSITIVE
Nonpregnant	25	5	20
Second trimester	23	6	26
Third trimester	64	23	36
At term	14	10	72

TABLE II. SEROLOGICAL RELATIONSHIP OF L. BIFIDUS IN MOTHERS AND INFANTS

	ANTIGENIC COMPONENTS[1]					
STRAINS	IIa.1	IIa.2	IIa.3	IIa.4	IIa.5	IIb.1
Thomas-R	0	40[2]	0	0	0	0
Thomas-R_2	320	0	0	640	0	0
Jourdan-R	0	0	0	0	0	0
Jourdan-R_2	0	20	0	0	0	0
Baby Jourdan-1	40	2,560	0	1,280	0	0
Baby Jourdan-2	0	2,560	0	0	0	0
Bell-R_2	0	0	0	0	0	0
Baby Bell	0	2,560	0	640	0	0

1. Schema of antigens after Williams and co-workers.[21]
2. Numbers are reciprocals of serum dilutions in which agglutination occurs.
R. Rectal culture of mother before delivery.
R_2. Rectal culture of mother after delivery.

Comment

That *L. bifidus* may be isolated from vaginal secretions of pregnant and nonpregnant women has been confirmed. There appears to be little reason to doubt that the organisms described in the present study belong to the same genus as those previously described in the stools of breast-fed infants. The colonies on agar plates and the morphology of the organisms in stained films were characteristic. Failure to grow aerobically and to produce molecular gas lends

support to this belief. Failure of the organisms to grow on the simplified medium of Hassinen and his associates[7] is also in agreement with later experience that strains of *L. bifidus* newly isolated from the stools of breast-fed infants generally require a more complex medium for growth.[21] The 4 strains requiring the addition of breast milk to the medium likewise resemble the strains isolated from infants' stools which require a supplement of breast milk.[6] The rapid conversion of a number of strains to aerobic straight rods producing molecular gas is characteristic of *L. bifidus*.[9] That only 3 vaginal strains were agglutinated in immune sera prepared from strains of organisms isolated from infants, however, might suggest to some a species difference between vaginal organisms and those in the stools of breast-fed infants, especially when 2 rectal strains from mothers were agglutinated by these sera. Since there are currently no other known differences between these groups, it is believed that this should be classified as a difference in type rather than as a difference in species. The importance of this difference, however, lies in the fact that rectal strains rather than vaginal strains may be the source of organisms which populate the colons of infants. If vaginal strains are the source, then it appears probable that antigenic changes in the organisms occur in the colon of the infant.

In the report of Williams and co-workers,[21] a system of nomenclature has been proposed for the labeling of antigenic components of *L. bifidus* and *L. parabifidus*. This system is followed in the present report to indicate the surface components revealed by agglutination reactions (Table II). In the cases reported by Williams and collaborators,[21] only 2 strains of *L. bifidus* were shown to have 2 surface antigens. These were JNX-11 and BLX-15 which are Baby Bell and Baby Jourdan in this report. Also in the present report, the rectal strain from the mother, Thomas, has 2 demonstrable antigens. This fact lends additional support to the hypothesis that the antigenic composition of *L. bifidus* is varied.[21]

It might be expected that a higher incidence of *L. bifidus* would be found if the results of stained films of vaginal secretions were included in the results of culture. There were of course instances in which bifid organisms were stained in the original film and in which *L. bifidus* was not isolated in culture. More often, however, *L. bifidus* was isolated in large numbers in culture without having been observed in the original film. The predominant organism was usually a straight gram-positive rod. Many of them were undoubtedly *L. bifidus*, but most were probably either the straight-rod mutants, so-called *L. parabifidus*, diphtheroids, or organisms generally classified as *L. acidophilus*. Some may even have been Clostridia. No effort was made to identify organisms other than *L. bifidus*. In any event, it appears that, although frequently numerous, *L. bifidus* is not ordinarily the predominant organism of the vaginal flora either normally or during pregnancy.

Employing the modified Teply and Elvehjem[9] medium either with or without a supplement of breast milk, the incidence of true bifid organisms is lower than that reported by Blaurock[3] with a liver infusion medium in both pregnant and nonpregnant women. Since the former medium is believed to be nutritionally superior, the explanation for this apparent discrepancy is not known. The result of our cultures at term, however, compares favorably with the incidence of *L. bifidus* reported by Montagna and Cataldi[8] in cultures taken during labor or immediately after delivery. The cause for the highly significant increase in incidence of *L. bifidus* which occurs only at term has not been determined.

Since the ages of the nonpregnant women were not comparable with those of the pregnant individuals, the objection might be raised that the former were not good controls. There was so little difference in the incidence of *L. bifidus* in the nonpregnant group and in the second trimesters of pregnancy, however, that this scarcely constitutes a valid criticism.

Summary

1. Vaginal cultures for *Lactobacillus bifidus* were obtained from 25 normal nonpregnant women, from 23 women in the second trimester of pregnancy, from 64 in the third trimester, and from 14 at term or overdue.

2. The incidence of *L. bifidus* in the nonpregnant and in the second trimester of pregnancy is about the same, with a mean of 23 per cent. The figures show a slight increase in the third trimester which is not significant. At term or beyond, however, there is a sudden highly significant increase in the incidence of *L. bifidus*. The cause of this phenomenon was not determined.

3. Only 3 of the vaginal strains of *L. bifidus* tested were agglutinated by any of the antisera previously prepared.

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THE BACTERIOSTATIC ACTIVITY OF pHisoHex ON THE VAGINAL FLORA*

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TECHNIQUES which have been employed to protect the parturient against puerperal infection include those which have as their objective the elimination or reduction of the bacterial flora of the vagina. Initially the therapy was topical in the form of vaginal instillations. Mayes[1] employed a mercurochrome method, while Soule and Brown[2] used a mercurochrome-iodine-glycerin combination and later 1 per cent neutral acriflavine in glycerin.

With the advent of chemotherapeutic drugs systemic rather than local therapy has been advocated for the prevention of intrapartum infection. Obstetrical conditions which have warranted the use of these agents include cases of prolonged labor, cases with a long period with ruptured fetal membranes, or those in which major obstetrical surgery is anticipated. Irrespective of the value of these drugs in reducing the incidence of infection of the amnion and its contents, there are limitations to their effectiveness and certain contraindications to their use. Further, the organism of potential pathogenicity frequently found in the generative tract may become resistant to or may not be affected by chemotherapeutic drugs. The anaerobic streptococcus and coliform groups are common offenders in cases which develop spontaneous infection even in the absence of obstetrical intervention. The use of antibiotics against the former both for prophylaxis and therapeusis is of limited effectiveness, while with the coliform group the routine prophylactic use of the specific antibiotic may be questioned. The pursuance of the latter policy may well lead to the production of resistant strains of organisms and thus impede subsequent antibiosis.

Relatively few of the studies of the bacterial flora of the female reproductive tract are in agreement. This lack of uniformity of findings is undoubtedly due to culturing of different areas, the methods of obtaining the cultures, variations in the culture procedures and the manner of classification of the bacteria. Soule and Brown[2] report differences in the frequency of anaerobic flora at various levels within the birth canal. Fewer positive anaerobic cultures of the cervix and upper vagina were obtained in contrast to those from the lower vagina and posterior fourchette. Recent studies have been concerned principally with cultures obtained from the upper portion of the vagina, more particularly from the posterior fornix.[3] The most common in-

*This study was made possible by a grant from the Department of Medical Research, Winthrop-Stearns, Inc., New York. N. Y.

habitants of this portion of the vagina when cultured were found to be aciduric bacteria, diphtheroids, yeastlike fungi, and not infrequently members of the staphylococcal and streptococcal groups.

In view of the effectiveness of a new detergent, pHisoHex,* used for surgical scrubbing, a study was undertaken to evaluate its effect on the bacterial flora of the vagina. pHisoHex has shown marked antibacterial action under other experimental conditions.[4-10] This communication concerns the bacterial content of the vagina of 177 patients with different obstetrical conditions before and after instillations of pHisoHex. These patients were selected from the outpatient and inpatient services of the Boston Lying-in Hospital. Five groups of patients were studied. Groups I and II were composed of ambulatory patients while Groups III, IV, and V were hospitalized patients. Those in Group III were under treatment for mild forms of pregnancy toxemia and Group IV was composed of those patients who entered the hospital with ruptured membranes, but not in labor. Finally Group V consisted of patients in active labor.

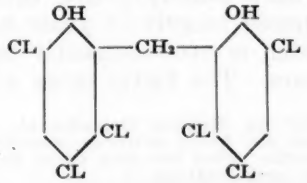
Procedures

Clinical Procedures.—The technique used for obtaining cervical cultures and for instillation of pHisoHex was the same in all five groups studied. The vulva was swabbed with a 1 per cent aqueous solution of Zephiran and a sterile bivalve speculum carefully inserted into the vagina. Cultures were taken from the external os of the cervix prior to each instillation of pHisoHex.

In Group I cultures were obtained from 38 patients supposedly in the last month of pregnancy at which time they made weekly visits to the clinic. Of this group, 15 delivered at the end of 2 weeks, 7 in 3 weeks, 6 in 4 weeks, 4 in 5 weeks, 5 in 6 weeks, and one patient made 8 visits before delivery. Each of the above had, at 7 day intervals, 5 c.c. of pHisoHex instilled vaginally. In Group II, 28 patients were instructed in a method of daily instillation into the vagina of 5 c.c. pHisoHex by the use of a special plunger-type applicator. Cultures were taken at weekly intervals when the patients reported to the clinic. Group III consisted of 31 house patients in whom cultures were obtained after self-instillation of pHisoHex made at 4-hour intervals during the day for a period of 24 to 48 hours.

Groups IV and V were treated under hospital aseptic technique. In Group IV, composed of 30 patients, an attempt was made to sterilize the vagina by instillations of pHisoHex twice daily. The 50 patients in active labor who comprised Group V received instillations every 6 hours throughout the day and night during the course of labor. Material for culture was ob-

*pHisoHex consists of a synthetic detergent, pHisoderm, reinforced with 3 per cent hexachlorophene (G-11) on a total weight basis. pHisoderm is composed of a sulfonated ether, petrolatum, lactic acid, and wool fat cholesterols. It has a pH value of 5.5. It has good emulsifying, sudsing, and dispersing properties and has been found to depress the surface tension of water more than soap. It is hypoallergenic. Hexachlorophene has the following composition: 2,2′ dihydroxy 3,5,6,3′,5′,6′, hexachlorodiphenylmethane. Its structural formula is:



tained just before delivery after the vulva and perineum had been prepared. A Sims speculum was passed posterior to the presenting part and cultures were obtained as near as possible to the posterior edge of the completely dilated cervix.

Bacteriological Procedures.—In all groups excepting Group V routine inoculations on culture media were made immediately after the cultures were taken. Two swabs were used, one for inoculating dry media, followed by a direct smear on a new clean glass slide for the Gram stain; the other swab was used to inoculate liquid media. In Group V, cultures which were obtained after 5 P.M. or before 9 A.M. were preserved by placing the swabs in test tubes containing 5 c.c. of 3 per cent peptone broth. Routine cultures were subsequently made from these tubes.

The following media* were routinely inoculated: blood agar plates and tryptophane broth were used for isolating aerobic organisms. Coliform bacilli were isolated on eosin methylene blue plates and fungi were grown on Sabouraud's medium. For the isolation of anaerobic bacteria duplicates of the blood agar plates and tryptophane broth indicated above were placed in jars and the anaerobic procedures of Brewer[11] or the Mueller-Miller[12] modification of Rosenthal were followed. Kulp's[13] tomato juice agar was used for the isolation of aciduric bacilli. Better growth was obtained when initial isolations were made anaerobically. For this reason these plates were also included in the anaerobic procedures just mentioned. Thioglycollate broth was used routinely and deep meat tubes were inoculated when anaerobic cultures were to be preserved for further study. All cultures were incubated at 37° C. except the Sabouraud which was kept at room temperature. Cultures were examined daily after 24 hours for bacterial growth. Anaerobic cultures and cultures on Sabouraud's medium were held for 10 days before being discarded when negative. The Gram stain was used to study the morphology and staining reactions and to make quantitative bacterial estimations. Fifty fields covering various portions of the slides were roughly recorded as 1 plus, 2 plus, 3 plus, 4 plus. The reductions noted occurred when the quantity diminished from 4 plus to 1 plus. A negative slide was so classified when fifty or more fields revealed a total absence of organisms.

Identification of the bacteria was made on the basis of their biochemical, morphological, and colonial characteristics.[14, 15, 16] Cultures of the staphylococcal groups were differentiated on blood agar plates and in broth. Sherman's description of streptococci, as applied by Dubos,[16] was used for their differentiation. Resistance to a temperature of 60° C. for 30 minutes and tolerance to 6.5 per cent of sodium chloride distinguished the enterococci from the other streptococcal groups. Anaerobic streptococci persisted only under anaerobic conditions and, when necessary, eosin methylene blue plates were used to identify the coliform bacilli and Russell's double sugar tubes were used for confirmation. Yeastlike fungi were frequently developed on other media in addition to Sabouraud's, especially the Kulp tomato juice agar. Diphtheroids were identified by their characteristic morphology and by colonial studies. The aciduric bacteria were isolated on Kulp's tomato juice agar. These organisms have as their common characteristic the ability to survive in concentrations of acid that usually prove fatal to nonsporing bacteria. The aciduric group is composed largely of yeast and the lactobacilli, including Döderlein's bacillus which is predominantly present in the vaginal flora during the reproductive years. The fairly large gram-positive rod of Döder-

*All media were prepared by the Medical Department of the Harvard Medical School. Media for routine agar plates and for broth cultures consisted basically of a tryptic digest of beef heart using Pfanstiehl trypsin. Five per cent horse blood was provided for blood agar plates. The broth contained 1 per cent dextrose.

lein was quite generally characteristic in the original Gram stain but cultures of these organisms exhibited marked pleomorphism. They varied in form from coccobacilli in diploids and in chains of diploids resembling streptococci, to filamentous, clubbed, curled, and spiral forms. Some also showed marked variations in staining. In addition to the anaerobic streptococci isolated, cultures of unclassified anaerobic micrococci were encountered. The Gram stain revealed gram-positive cocci of variable sizes, not in any typical arrangement. The colonies on blood agar plates were small, nonhemolytic, and colorless. Subcultures produced meager and unsatisfactory growth for further studies. The slow-growing gram-negative pleomorphic rods were the distinguishing feature of the anaerobe, Bacteroides. Fusiform bacilli were identified by their characteristic morphology, i.e., long, slender gram-negative rods with tapering ends. These organisms were difficult to grow on artificial media and required anaerobic conditions.

Results

The original cervical cultures from 177 patients studied are listed in Table I. The results of these cultures are more in agreement with the findings of Hesseltine.[3] Attention is drawn to the infrequency of anaerobic streptococci.[2] Brown has pointed out the variations in the incidence of anaerobic flora which are obtained when cultures are taken from the cervix rather than from other areas of the vagina. In Table II are listed the organisms found in the original cervical cultures in the different groups in contrast to the cultures taken at the completion of the pHisoHex instillations. With the exception of the coliform group there was a general reduction in the bacterial flora of the cervix. It will be noted that the cocci and anaerobic bacteria were particularly affected. The instillation of pHisoHex gave variable results depending on how the material was administered. Groups I and II were not materially affected, whereas in Groups III, IV, and V, a reduction in bacterial growth was observed. In Group III, the elimination of the anaerobic bacteria is particularly significant. The incidence of *B. coli* associated with this investigation is recorded in Table IV. Groups II and III showed an increase in the frequency of this organism while Groups IV and V revealed a decrease. It will be noted that beta hemolytic streptococci of the Lancefield Group A were not encountered in this study.

TABLE I. INCIDENCE OF BACTERIAL GROWTH IN THE FIRST CERVICAL CULTURE FROM 177 PATIENTS

BACTERIA	NUMBER OF CULTURES
Aerobic.—	
Staphylococci	
Albus	44
Aureus	13
Streptococci	
Viridans	17
Nonhemolytic	13
Enterococci	25
Coliform group	14
Diphtheroids	47
Aciduric s	108
Yeastlike fungi	48
Anaerobic.—	
Streptococci	6
Micrococci	5
Bacteroides	4
Fusiform	4

TABLE II. EFFECT OF pHISOHEX INSTILLATIONS ON THE BACTERIAL CULTURES FROM THE CERVIX

	GROUP I		GROUP II		GROUP III		GROUP IV		GROUP V	
TOTAL NUMBER OF PATIENTS	BEFORE 38	AFTER 38	BEFORE 28	AFTER 28	BEFORE 31	AFTER 31	BEFORE 30	AFTER 30	BEFORE 50	AFTER 47*
Aerobic Bacteria.—										
Staphylococci										
Albus	17	8	11	6	6	3	6	2	4	1
Aureus	0	0	1	0	3	1	1	1	8	0
Streptococci										
Viridans	4	3	4	2	6	0	2	0	1	1
Nonhemolytic	3	3	1	0	3	1	2	0	4	0
Enterococci	8	6	4	1	5	0	2	1	6	1
Coliform group	0	0	0	16	5	13	4	5	5	2
Diphtheroid	7	4	13	6	7	1	2	1	18	6
Aciduric	28	24	21	14	19	9	12	6	28	10
Yeastlike fungi	16	13	12	9	5	5	4	3	11	6
Anaerobic Bacteria.—										
Streptococci	2	0	1	0	2	0	1	0	0	0
Micrococci	2	0	0	0	2	0	0	0	0	0
Bacteroides	0	0	1	1	3	0	0	0	0	0
Fusiform	2	2	0	0	0	0	2	0	0	0

*Three were delivered by cesarean section.

TABLE III. THE EFFECT OF pHISOHEX ON THE INCIDENCE OF BACTERIAL GROWTH

GROUP	I	II	III	IV	V
NUMBER OF PATIENTS	38	28	31	30	50
As Indicated in Culture Media.—					
Bacterial growth occurred	38	28	25	19	35
Alteration of flora	0	5	11	6	18
Vagina rendered sterile	0	0	6	11	15
As Indicated in Stained Slide.—					
Reduction in bacterial count	5	14	19	11	22
Bacteria present	37	28	29	14	32

TABLE IV. INCIDENCE OF B. COLI

GROUP	I	II	III	IV	V
NUMBER OF PATIENTS	38	28	31	30	50
Positive before treatment	0	0	5	4	5
Became negative during treatment	0	0	1	1	3
Became positive during treatment	0	16	9	2	2

Summary

The results of this study indicate that pHisoHex will control the growth of certain bacteria. Its effectiveness was most consistent among gram-positive cocci and anaerobic bacteria, the more frequent offenders in puerperal infection. The coliform group which may also incite puerperal infections was less affected by the detergent. Actually when pHisoHex was self-administered positive cultures for these organisms increased. Hence, the hazard of coliform invasion of the vagina in self-administered therapy is a definite one. When frequent instillations were performed under aseptic precautions, marked re-

duction in coccal forms of bacteria was observed. In approximately 34 per cent of the patients who received this type of treatment, vaginal cultures became sterile.

It is well recognized that potential pathogens such as aerobic and anaerobic streptococci are best maintained in a media at a constant pH which approaches that of blood. Therefore, the bacteriostatic effect of the detergent pHisoHex undoubtedly involves a reduction of the vaginal pH as well as the antibacterial action of the substance itself.

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EVALUATION OF THE SIMULTANEOUS USE OF CYTOLOGY AND BIOPSY IN THE DIAGNOSIS OF CARCINOMA OF THE CERVIX*

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IT HAS been a standard practice to use both cytological smears and biopsy to obtain a positive diagnosis in suspected cases of carcinoma of the cervix uteri. However, the usual practice is to use one or the other alone during the initial examination, resorting to the one not already used to obtain corroborative evidence. Believing that prompter and more definitive diagnoses might be obtained by using both methods at the first examination, we undertook a study of 500 new patients admitted to the Cook County Out-Patient Gynecological Clinic, with a view to ascertaining the accuracy of the diagnoses of cervical carcinoma by an initial routine of combined use of cytology smear and biopsy.

Previously one of us (M. W. R.) had made a study of some 6,000 cytological smears,† most of which had been taken as a "screening" prior to biopsy; during this study, discrepancies were noted. In some instances, the cytology was apparently in error, while in others, the error appeared in the biopsy. However, in some of these, when the biopsy was repeated, it was found to be in agreement with the earlier cytology. These observations suggested the present study, especially in view of the fact that, in some of these cases, the final result was the diagnosis of a carcinoma which was clinically unsuspected.

We had abundant precedents for the use of both methods, since many earlier workers have concluded that these types of studies are valuable diagnostic aids in the detection of carcinoma of the uterus, especially of the cervix. Lock and Caldwell[9] performed 1,797 biopsy examinations on cervices that deviated from the normal, finding 9.2 per cent indicative of cervical carcinoma. Beclere[2] obtained closely similar results; 790 clinic patients yielded 9.4 per cent positive readings. Whichever their preference, all workers agree that a cytological diagnosis of carcinoma should be confirmed by biopsy, with the final diagnostic criterion being the histological diagnosis.

Procedure

In any patient whose cervix was eroded, unhealthy, or in any way suspicious in appearance, both smear and biopsy were taken at the initial examination, this work being confined to new patients seeking admission to the

*This investigation was supported by a research grant from the Dr. Jerome D. Solomon Research Foundation, Hektoen Institute for Medical Research.

†To be reported later.

clinic. The number so checked represents about 20 per cent of the total admissions for the period covered. Patients with a history suggestive of carcinoma (e.g., contact bleeding, menorrhagia, abnormal discharge), as well as those with gross signs of carcinoma, were given especially careful study. In each instance, the smear was taken first.

Evaluation

In evaluating the diagnoses, the standard terms "false positive" and "false negative" have been used to describe a report found to be at variance with others. In this study, the biopsy "false negatives" were shown up by the positive cytology, in which case a second biopsy was requested. The latter would be found positive.

Most cytologists have found fewer and fewer false positives as their experience increased. Graham and Meigs[6] report their latest figures at 0.04 per cent. Their false negatives, by far the more dangerous of the two because of the false sense of security they give to both physician and patient, did occur in about 10 per cent of cases in both biopsy and cytology methods. This figure, too, has declined with increase in experience. Botsford and Tucker[2a] found that 40 out of 43 cases of carcinoma of the cervix were correctly diagnosed by one vaginal smear, while the remaining 3 were confirmed by biopsy. Thirty-eight of these had been suspected from the clinical symptoms. They also found that immediate fixation of the smear was of utmost importance. Other workers report that, in dealing with in situ carcinoma, the incidence of biopsy false negatives was higher, occurring in 30 per cent, as against 12.5 per cent for cytological diagnosis. Interestingly enough, and as confirmation for our belief, when both methods were used together, the percentage of error fell off to 1.7 per cent.[6]

Technique

The cytological smear was obtained as follows:

The cervix was exposed by dry speculum. Using an Ayre wood spatula and a cotton swab, material was obtained from the external os, the squamocolumnar junction or the junction of the erosion and normal tissue, or the edges of the lesion, and from the posterior fornix. Two frosted-end slides were labeled and smeared, and placed immediately in a fixative containing equal parts of ether and 95 per cent alcohol (ethyl or isopropyl). There they were allowed to remain for at least 30 minutes; they were then stained according to the method of Papanicolaou[10] and read by one of us (M. W. R.). The report was divided as follows:

I. No abnormal cells.

II, A. Atypical cells, probably inflammatory.
B. Atypical cells, with active nuclei suggestive of malignancy.

III. Suspicious—cells with malignant features.

IV. Positive for malignant cells.

V. Absolute evidence of malignant cells.

Following the taking of the smear but at the same examination, several (2 to 4) punch biopsies were taken from the suspected areas, or from the squamocolumnar junction, put into 10 per cent formalin and prepared and stained (with hematoxylin and eosin) according to routine pathology technique. The Schiller test was used as an aid to demarcate normal from abnormal tissue. These biopsies were read by Dr. A. Ragins, Cook County Hospital Surgical Pathologist, and divided as follows:

I. If positive, usually "infiltrating squamous-cell carcinoma" with notes on differentiation and whether "early" or not.

II, A. "Suggestive of possible early carcinoma, please repeat biopsy." (Usually based on dispolarity, atypical nuclei, or hyperchromatism.)

B. Intraepithelial metaplasia. (This pathologist does not adhere to the idea of carcinoma in situ or preinvasive carcinoma, but does reveal that his diagnosis of "intraepithelial metaplasia" may correspond to the former terms "intraepithelial carcinoma," etc.)

III, A. If negative (for carcinoma), cervicitis or endocervicitis, usually chronic and with or without erosion.

B. Normal portio vaginalis or cervix.

C. No evidence of malignancy in this specimen.

In the 500 patients represented in this series, ages ranged from 15 to 80 years, with an average of 33.2 years. Reasons for administering the set of tests were

Cervical "erosion" alone	412
History plus "erosion"	71
History alone	17

Interpretation of Reports

Those biopsies which were reported as definite squamous carcinoma were the only ones considered, for purposes of this study, as definitely positive. Reports either suggestive of carcinoma or of intraepithelial metaplasia were not considered as a definite positive diagnosis. When intraepithelial metaplasia was reported, it was felt that a possible in situ carcinoma might be present, although it was not recorded or classified as such. There are no pathological diagnoses of in situ carcinoma in this series because of the above-indicated fact that our interpreting microscopist (pathologist) does not adhere to that diagnosis. At times, the terms "early" or "very early infiltrating" are used instead. Reports occasionally contained a combination of two or more diagnoses; these will be discussed later.

TABLE I. BIOPSY—ANALYSIS OF REPORTS

BIOPSY REPORTED AS	NO. OF CASES	%	AVERAGE AGE (YEARS)
Negative. (No Carcinoma).—			
A. No evidence of malignancy	42	8.4	34
B. Normal portio vaginalis or cervix	14	2.8	35
C. Cervicitis, or endocervicitis, with or without erosion	394	79.0	31
Total normal	450*	90.2	33.3
Positive (for Carcinoma).—			
True positive, squamous carcinoma	35	7.0	47
Suggestive Positive.—			
A. Originally reported "suggestive" (Subsequent biopsy positive)	3	0.6	44
B. Intraepithelial metaplasia (Subsequent biopsy positive)	5	1.0	33.6
Total positive	43	8.6	41.5

*Includes one case where biopsy and cytology were both negative on first reading, both positive on second reading.

The only cytological reports that may be considered important as suggesting and/or making for a diagnosis of carcinoma were those that fell into Groups II, B, III, IV, or V (see above). The latter three groups are the actual

positives. Group III is very suspicious for malignancy. Group II, A is that in which active cells, some with features suggestive of malignancy, were found. Not all cases received a report in only one group; in some, cells showed gradations of abnormality, giving such group combinations as II, A and III or III and IV, for example. Those reports that did not suggest malignancy were the ones in which there were found (a) no abnormal cells and (b) atypical cells, probably inflammatory.

TABLE II. BIOPSY—CORRELATION WITH CLINICAL AND PHYSICAL FINDINGS

BIOPSY REPORT SHOWED	NO. OF CASES	CERVIX ERODED OR SUGGESTIVE, I.E., GRANULAR, ULCERATED, ETC.	HISTORY SUGGESTIVE OF CARCINOMA
Negative.—			
1. Cervicitis or endocervicitis with or without erosion	386	380	36
2. Normal portio vaginalis, or cervix	14	11	4
3. No evidence of malignancy	42	40	14
Total	442	431 (93.3%)	54 (12%)
Suggestive.—			
4. A. Suggestive of carcinoma	3	3	3
B. Intraepithelial metaplasia	9	5	3
Total	12	8 (100%)	6 (75%)
Positive.—			
5. A. Squamous carcinoma (also cytology positive)	26	26 (100%)	19 (73%)
B. Where only one or other (cytology or biopsy) was originally positive	16	14 (87.5%)	7 (43.7%)
Total	42	40 (95%)	26 (62%)
Not Included in Original Series as Positive.—			
6. Adenocarcinoma (Gartner's duct origin?) Unusual case in this series	1	1 (100%)	1 (100%)
7. Squamous carcinoma (both cytology and biopsy in error)	1	1 (100%)	1 (100%)

TABLE III. CYTOLOGY—ANALYSIS OF REPORTS

CYTOLOGY REPORTED AS	NO. OF CASES	PER CENT
Negative.—		
I. No abnormal cells	335	67.0
II, A. Atypical cells, probably inflammatory	72	14.4
II, B. Atypical cells with active nuclei or suggestive of malignancy	46	9.3
Positive (for Carcinoma).—		
III. Cells with malignant features IV. Positive for malignant cells V. Absolute evidence of malignancy	48*	9.6

*Includes one case where both biopsy and cytology were negative on first reading, positive on second reading.

Comparing the two types of reports, we find that the positive biopsy reports number 42 (8.4 per cent), the positive cytology reports 48 (9.6 per cent). However, if those biopsy reports that state "intraepithelial metaplasia" or "suggestive of carcinoma" are included, the biopsy figure increases to 54 (10 per cent).

Analysis of False Negatives

When a proved carcinoma was missed by one or other of the two methods, the erring report was designated a false negative. Such false negatives were found in both sets of reports.

TABLE IV. CYTOLOGY—CORRELATION WITH CLINICAL AND PHYSICAL FINDINGS

CYTOLOGY REPORT SHOWED	NO. OF CASES	WITH CERVIX SUGGESTIVE, I.E., ERODED, GRANULAR, ULCERATED, ETC.	WITH HISTORY OF IRREGULAR BLEEDING
Negative.—			
I. No abnormal cells	335	328	33
II. Atypical cells, probably inflammatory	72	69	15
Total	407	397 (97%)	48
Suggestive.—			
II, B. Atypical cells with active nuclei or suggestive of malignancy	46	41 (88%)	12
Positive.—			
III. Cells with malignant features	16	14 (87%)	8
IV. Positive for malignant cells	12	12 (100%)	9
V. Absolute evidence of malignancy	20	20 (100%)	16
Total	48	49 (96%)	33
Addendum			
Adenocarcinoma (Gartner's duct origin?)	1	1	1
Squamous carcinoma (both cytology and biopsy in error)	1	1	1

Biopsy False Negatives.—

The figures analyzed in the following are based upon 43 cases of proved carcinoma (from subsequent biopsy reports).

TABLE V. BIOPSY FALSE NEGATIVES

BIOPSY REPORT	NO. OF CASES	% ERROR	AVERAGE AGE (YEARS)	CORRESPONDING CYTOLOGICAL REPORT (POSITIVE)
1. Negative, definite	4	9.2	31.2	Gr. III, 1 Gr. IV, 1 Gr. V, 2
2. Negative, questionable		4.6		Gr. IV, 1
A. Suggestive of carcinoma	2	4.6	42.5	Gr. V, 1
B. Intraepithelial metaplasia	5	11.6	33.6	Gr. III, 1
Total	11		36.4	Gr. V, 4

The group of biopsies in Table VII, B, reported as suggestive of carcinoma, is also interesting. While each such report requested a repeat biopsy, this was not necessarily taken as evidence of carcinoma, hence the classification as negative.

Cytology False Negatives.—

It is interesting to note that two of the cytology false negative cases were very early clinical carcinoma. The other two were clinically definite, and ordinarily would have aroused clinical suspicion from the physical findings. In these last two cases, resmears were requested; one of the two contained many red blood cells, a factor conducive to error.

If we are to consider the biopsy and cytology reports of negatives as the only true error, then our figures would be (a) 4 for biopsy, or an error of 9.3 per cent, and (b) 2 for cytology, or an error of 4.6 per cent.

Comparing the average ages of the patients with false negatives under both methods, it will be noted that the true negative was found in a much younger group in both instances (biopsy, 31.2 years; cytology, 23 years).

TABLE VI. DETAILED ANALYSIS OF BIOPSY FALSE NEGATIVES DEFINITELY NEGATIVE (4 CASES)

BIOPSY REPORT (DETAIL)	AGE (YEARS)	CLINICAL HISTORY	APPEARANCE OF CERVIX	CYTOLOGICAL DIAGNOSIS	REBIOPSY	CLINICAL GRADE
Slight endocervicitis; 2 months later the same	21	Pain, lower right quadrant	Mild erosion	Gr. III (3 reports), "small focus, may be squamous carcinoma	(5 months later) "early squamous carcinoma"	I
Small fragment of portio vaginalis. D. & C. 1 month later negative	50	Postcoital bleeding 4 months. Menop. 3 years before	Irregular, slight erosion	Gr. IV and V (positive)	Squamous-cell carcinoma 2 months later	I
Fragment of portio vaginalis	26	Pain in lower abdomen	Erosion, both lips	Gr. IV and V, "may be early and small"	Early infiltrative squamous carcinoma 1 week later	I
Chronic endocervicitis with healing erosion	28	Pain in lower abdomen and right leg	Eroded nodular	Gr. III and IV, "may be early carcinoma cervix"	Early infiltrative squamous-cell carcinoma 2 months later	=
Average age	31.2					
(excluding 50 year old)	25					

TABLE VII. DETAILED ANALYSIS OF BIOPSY FALSE NEGATIVES
QUESTIONABLE NEGATIVE

BIOPSY REPORT (DETAIL)	AGE (YEARS)	CLINICAL HISTORY	APPEARANCE OF CERVIX	CYTOLOGICAL DIAGNOSIS	REBIOPSY	CLINICAL GRADE
A. Intraepithelial Metaplasia (5 Cases).—						
Chronic cervicitis. Portio vaginalis shows moderate intraepithelial metaplasia	32	Bleeding, 1 month	Degenerative	Gr. IV and V	Infiltrative squamous-cell carcinoma with hornification 1 week later	II
Chronic endocervicitis with metaplasia of portio. Repeat biopsy	37	Pain, lower abdomen	Posterior lip granular	Gr. IV and V	Early infiltrative squamous-cell carcinoma 3 weeks later	I
Leukoplakia of portio vaginalis with intraepithelial metaplasia	27	Pain, lower abdomen	Leukoplakia "spot" on anterior lip	Gr. III, believe this very early squamous carcinoma	Healed cervical erosion. One week later early squamous-cell carcinoma if clinically doubtful please rebiopsy	0
Chronic endocervicitis. One area portio vaginalis intraepithelial metaplasia with severe inflammation	30	Pain, lower abdomen, leukorrhea	Moderately eroded, lacerated	Gr. III, believe this comparable to carcinoma in situ	3 weeks later early infiltrative squamous carcinoma with intraepithelial metaplasia	I
Chronic endocervicitis, nests of epithelial cells, characteristic of intraepithelial metaplasia of portio vaginalis	42	Leukorrhea	Eroded, granular, bleeds easily. Suspicious area 6 o'clock	Gr. IV and V	2 weeks later, early infiltrative squamous carcinoma with rudimentary hornification	I
Average age	36					
B. Suggestive of Carcinoma (2 Cases).—						
Chronic endocervicitis. In 1 corner, nest suggestive of tumor tissue. Please repeat biopsy	52	Dysuria	Granular, friable area at 6 o'clock	Gr. IV and V; definite for squamous type	1 week later, scattered nests of squamous epithelium with large, deep-staining, irregular nuclei, suggestive of tumor cells. Please repeat biopsy. 2 weeks later, chronic endocervicitis and early squamous-cell carcinoma	I
Severe chronic endocervicitis with embedded nests of large cells, irregular deep-staining nuclei, diagnostic of tumor cells. Please repeat biopsy	33	Moderate irregular bleeding, 6 weeks	Small irregular ulcer with overhanging edges	Gr. III and IV	2 weeks later, infiltrating nonhornifying squamous carcinoma	I
Average age	42.5					

TABLE VIII. CYTOLOGY FALSE NEGATIVES

CYTOLOGY REPORT	NO. OF CASES	% ERROR	AGE (YEARS)	AVERAGE AGE (YEARS)	CORRESPONDING BIOPSY REPORT
Gr. I	2	4.6	21	24	Chronic endocervicitis, infiltrating squamous-cell carcinoma of connective tissue stroma
			27		Early infiltrating squamous-cell carcinoma
Gr. II, A	1	2.3	43		Infiltrating moderately anaplastic squamous-cell carcinoma with inflammatory changes
Gr. II, B	1	2.3	45		Infiltrating moderately anaplastic squamous-cell carcinoma
Total	4			37.3	

TABLE IX. DETAILED ANALYSIS OF CYTOLOGY FALSE NEGATIVES

CYTOLOGY REPORT (DETAIL)	AGE (YEARS)	CLINICAL HISTORY	APPEARANCE OF CERVIX	CYTOLOGY FOLLOW-UP	CLINICAL GRADE
Gr. I, definitely negative	21	Delivered twins 3 weeks previously	Slight erosion	Resmear negative; patient did not return	I
	27	Negative	Negative. Suspicious area endocervical region; no bleeding	Resmear; Gr. IV	I
Gr. II (too many r.b.c.; please resmear)	43	Contact bleeding several months	Clinical carcinoma. Cervix hard, irregular bleeding lesion	None	III
Gr. III, suggestive. Some large multinucleated cells. Biopsy, resmear	45	Irregular bleeding, 10 weeks	Clinical carcinoma, hypertrophy, cauliflower papillary, nodular	None	II
Average age	33.3				

TABLE X. AGE COMPARISON

	NO. OF CASES	AVERAGE AGE (YEARS)
A. Biopsy False Negatives.—		
1. "True" false negative	4	31.2
2. Questionable		
A. Intraepithelial metaplasia	5	36.0
B. Suggestive of carcinoma	2	42.5
Total		34.6
B. Cytology False Negatives.—		
1. "True" negative	2	23.0
2. Questionable negative	2	44.0
Total		33.3

In the questionable false negatives, the average ages were, for biopsy, 39.2 years, and for cytology, 44 years.

From Table X it would appear the true negative and the intraepithelial metaplasia diagnoses, if counterchecked by a positive test of the opposite type, will probably occur in a younger person and will be given by an earlier lesion.

Cytology False Positives

There were six such cases for a percentage error of 1.2 per cent. These may be divided into two groups:

1. Where the biopsy was not strictly negative but rather was construed as questionable. Nevertheless, such reports were considered as false positives, though we may really consider them questionable false positive.
2. Where the biopsy was definitely negative.

In the first group (the questionable negatives) there were 2 cases for a total of 0.4 per cent of the entire series; in the second group (definitely negative), there were 4 cases for a total of 0.8 per cent of the series.

The biopsy false negatives which were classified as questionable were those in which the biopsy report was either intraepithelial metaplasia (5 cases) or suggestive of tumor cells or carcinoma (2 cases). As mentioned earlier, we were guided by the accepted standard for diagnosis for squamous-cell carcinoma of the cervix in our clinic, that of "infiltrating squamous carcinoma," thus stated in positive terms. Yet we could not but be impressed with the interesting coincidence of intraepithelial metaplasia and squamous-cell carcinoma. One will readily note that, out of five such cases, only one gave a suggestive clinical history, and this patient was found to have a Group II carcinoma! The rest all had early carcinomas, one being listed as Group 0.

While it is, of course, not known just how cancer arises, it might be felt that it probably starts as a small focus of cells, slowly and intraepithelially. This focus may remain in situ, growing very slowly, and continuing quiescent for five or even ten years before overt invasion.[7] It may even regress.

It is also known that a surface (in situ) and an invasive lesion may coexist in the same individual. Cases[7] have ben followed which started as surface lesions and then went on to become frank carcinomas.[13] In the presence of a report of intraepithelial carcinoma, one must look further to see if there is not another area that is already invasive. Since the squamocolumnar junction is accepted as the common site for early development of these lesions, it can readily be understood why the surface cytological smear at this point would be an excellent means of obtaining significant cells when the lesion is in its infancy. Thus our two cases of intraepithelial metaplasia might conceivably eventuate into true squamous-cell carcinomas. One of these had had three persistently positive cytological diagnoses. These two are now being carefully followed.

As in the case of the false negatives, it will be noted that the average age is rather low in the group of definite false positives; also that in only two of the six cases did the cytological diagnosis fall into Group IV (i.e., positive for malignant cells, a more definite positive).

Two other cases of carcinoma were found in this series. These are reported separately. One was an adenocarcinoma, probably of Gartner's duct origin, the other a squamous-cell carcinoma of the cervix. The latter was missed initially by both biopsy and cytological smear, but subsequently both tests were positive. This case was a clinical Group II carcinoma with much bleeding and inflammatory changes. The Gartner's duct carcinoma yielded a negative smear but was positive by biopsy. The smear here was obscured by 4-plus red blood cells; the report read "atypical with active glandular cells; please resmear."

Comment

In the diagnosis of carcinoma of the cervix both diagnostic methods, namely, biopsy and cytological examination of cervical-vaginal smears, are

extremely valuable in arriving at a conclusion. That there is inherent possibility of error in either method is apparent. These errors arise in the main, no doubt, from mechanical causes. A poor biopsy specimen might be one in which (a) there was an inadequate amount of tissue, (b) there was no neighboring "normal" tissue, (c) the pathological area was not represented, or (d) it was impossible to ascertain the site of pathology (e.g., very early lesions). By the same token, cytology smears also may be misleading. Too numerous red blod cells (from oozing or bleeding), infected and/or advanced tumor (pus and degenerative material), and the like, all lead to errors in this field. Gates and associates[4] state that "it is easier to recognize malignant cells exfoliated from early tumors than those from advanced growths, since superficial necrosis is apt to occur when the tumor is well developed, thus obscuring the malignant characteristics of the cells." It is also known that inflammatory conditions will give rise to misleading changes in the cells. Ferguson[3] noted this in the presence of ulceration, infection (e.g., trichomoniasis), and sometimes in pregnancy. Changes in the nuclei, showing activity akin to that found in malignant tumors, may also occur in many nutritional, degenerative, inflammatory, radiational, and reparative processes.

It is instructive to observe that so many of the lesions in our series were found to be in Stage I (Schmitz). As a rule, cases so listed comprise about 1.3[14] to 15 per cent of any given series; we found 19 out of 43, for an incidence of 44 per cent, a significant increase. Twenty-eight of the 43 were revealed by the combined tests of which 9 were in Stage I; the false negative, after reevaluation, yielded the remainder. Eight patients, with an average age of 27 years (2 were only 21), or 18 per cent of all those found to have carcinoma, would not have aroused any clinical suspicions had not the criteria of erosion, etc., been used. These could be classed as clinically asymptomatic.

It is the early carcinoma that is amenable to treatment. It seems reasonably apparent from this study that these Stage I carcinomas may be detected much more frequently than is usually taught (i.e., 5 to 15 per cent) by using both methods of examination simultaneously. In our series, three times as many (44 per cent as stated) were detected while still in this early stage of development when simultaneous cytological smear and multiple punch biopsy were employed routinely. The simple, eroded cervix is certainly commonplace enough; in the absence of other clinical signs, it may be considered reason enough for ruling out early carcinoma. We feel that more attention to these eroded cervices, especially if other suggestive symptoms are found, regardless of the age of the patient, would help to reveal many early lesions, often even in the preinvasive stage. Such studies are within the facilities of every physician's office, and should be done routinely.

The cytological smear alone seems to be quite sensitive and an excellent method of screening, but a positive smear, even in the face of a negative biopsy, fairly demands a careful follow-up within a few weeks, with a rebiopsy in several months at the longest.

It will be noted that initial biopsy revealed carcinoma in 31 cases, or 70 per cent of the total. Initial cytological smear revealed invasion in 38 cases,

or 82 per cent. In the biopsy group there were 4 definite false negatives, in the cytology group, 2, for errors of 9.3 and 4.6 per cent, respectively. When both test methods were used, there was only 1.7 per cent of error.

Our experience in this series of cases leads us to observe that the cytological method is the more sensitive and led to more eventual positive diagnoses. Most of the smears were taken by the writers, who were careful to obtain material from the cervix and vagina (as outlined previously). This proved very helpful. Further, we believe that the surface, circumferential smear is very thorough, as it will obtain material from every possible sector of the exocervix, squamocolumnar junction and/or junction of erosion and normal tissue, thus revealing even the occasional and very early carcinoma cell.

Conclusions

1. Squamous carcinoma of the cervix may be diagnosed in the Outpatient Clinic by the combined use of the two diagnostic methods, (1) cytological cervicovaginal smear, and (2) multiple punch biopsy.

2. Routine use of both methods at the initial examination on cervices showing some form of lesion (such as erosion), or having a possible suspicious history, revealed 43 cases of squamous carcinoma in 500 patients examined.

3. Initial cytological smear diagnosis compared very favorably with the initial biopsy diagnosis, cytology yielding 41, and biopsy 39 cases.

4. The false negatives of one test were revealed by the positives of the other.

5. Twenty-eight patients, with an average age of 47 years, had initial positives with both methods. Nine of these cases (average age of the patient 37.3 years) were classed in Stage I.

6. Fifteen cases were discovered by one method or the other. Ten of these were classed in Stage I.

7. Eight (8) cases of the entire series of 43 were clinically asymptomatic.

8. Routine screening by biopsy or cytological smear tests should be done on all eroded or suspicious cervices regardless of clinical history.

9. The cytological cervical smear may be done quite easily and appears to be the more sensitive of the two tests, especially in early carcinoma.

10. It is conceivable that either routine test, whether the cytological or biopsy, will yield a great number of carcinomas in Stage I.

11. Since the cytological smear is the more simple to take of the two, it is advocated that it be used routinely on all eroded or suspicious (in appearance or by history) cervices.

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COMPARATIVE CYTOLOGIC STUDIES OF VAGINA, URINARY SEDIMENT, AND BUCCAL MUCOUS MEMBRANE IN NEWBORN INFANTS*

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IT HAS long been known that the newborn infant has a high concentration of estrogenic hormone in the blood as a result of transmission of estrogen from the mother and the placenta to the fetus. The high estrogen level rapidly decreases from approximately 80 mouse units per 100 c.c. of blood at birth to almost zero within 10 days from birth.[10] In response to the falling estrogenic titer, the epithelial lining of the vagina of the newborn girl undergoes, during the first few days of life, a series of modifications which have been demonstrated by daily smears of the vagina.[5] The mucosa is at first relatively thick with abundant layers of epithelial cells, and then becomes quite thin because of desquamation of most of these cells.

More recently, a correlation has been shown in adults between smears of urinary sediment and of the vagina, as well as between oral and vaginal smears. Papanicolaou,[8] in examining urine of men receiving estrogen therapy for prostatic carcinoma, noted changes in the cytology of the urinary sediment quite similar to changes in vaginal cytology that take place during estrogenic stimulation. The parallelism of the cytologic cycle of the urinary sediment and vaginal epithelium was clearly demonstrated by Del Castillo[3] in 1948. A similar relation has also been demonstrated to exist during pregnancy.[6, 9] Ziskin and Moulton[12] have recently observed that oral and vaginal epithelia show parallel changes in the degree of cornification accompanying the menstrual cycle, during estrogen treatment, and in deprivation states.

Although the studies cited show that the epithelium of the vagina, urinary tract, and buccal mucous membrane are all sensitive to alterations in the estrogenic level, it is generally agreed that the vagina is the most responsive and the buccal mucous membrane the least sensitive.

Normal Vaginal Cytology

A brief review of the characteristics of the epithelium of the normal vagina will be helpful in evaluating the results of the present report. The exfoliated cells of the urinary tract and buccal mucous membrane easily fit into the known classifications of cell types found in the vaginal smears.[1, 2, 7] De Allende and Orias,[2] using the trichromatic stain of Shorr,[11] distinguish two main groups of cells, cornified and uncornified, as described in the following paragraphs:

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A. The cornified cells represent the maximum differentiation of the epithelium to estrogen. Since their two chief characteristics are acidophilic staining and pyknotic nuclei, they are called cornified karyopyknotic cells. Of these, two cell types can be demonstrated, as follows:

1. Those from the superficial layers of the vagina, which are especially preponderant in the presence of high estrogenic hormone levels. They are characterized by large size, polygonal shape, thinness, smooth edges, and an orange-red, homogeneous, transparent cytoplasm, as well as by the small pyknotic nucleus.
2. Those cells from the deeper layers, appearing only when the estrogen level is very high, are similar to those of the superficial layers, but contain coarse, deep red or violet granules in the cytoplasm. They are called granular cornified cells.

B. Uncornified cells which progress from the surface toward the base of the vaginal epithelium can be classified as (1) karyopyknotic uncornified cells, (2) intermediate, and (3) deep cells. All stain blue or shades of blue green.

1. Karyopyknotic uncornified cells are morphologically similar to the cornified cells, and appear in the presence of a fairly high estrogen level. They are about to become cornified and are characterized by pyknotic nuclei which may be either central or slightly eccentric, and clear blue or blue-violet cytoplasm which may contain fine or coarse granules.
2. Intermediate cells, representing a transition between the round cells of the deep layers and the larger karyopyknotic cells of the more superficial layers, come from the intermediate layers of the vaginal epithelium. Their presence indicates a moderate-to-low level of estrogen. They present a great diversity of appearance but in general are recognized by the following characteristics: large size, polygonal or flat shape, homogeneous, transparent cytoplasm staining clear blue or violet, and a large nucleus having a well-differentiated chromatin net.
3. Deep cells are seen chiefly with a very low estrogenic hormone level. They are small, round or ovoid, and stain clear blue or violet. Their characteristic feature is a large, central nucleus containing a well-differentiated chromatin net.

Purpose of Present Study

This investigation was undertaken to determine the characteristics of the exfoliated epithelium of the vagina, urinary tract, and buccal mucous membrane in newborn infants, and to correlate the cytologic changes both with the falling estrogenic level and with each other.

Methods

The experimental subjects were 25 unselected newborn infants consisting of 13 males and 12 females. Vaginal, buccal and urinary sediment smears were taken from the females, and buccal and urinary sediment smears from the male newborns. Smears were taken from each infant on alternate days from the first until the seventh or eighth day after delivery, at which time the babies were discharged from the hospital. Four sets of smears were obtained from each infant, totaling 244. All smears were personally studied by the author.

Vaginal smears were obtained by lightly passing a small, dull, spoon-shaped spatula over the upper two-thirds of the posterior vaginal wall and by spreading the material thinly on a clean slide which was immediately immersed in a fixative of equal parts of ether and 95 per cent alcohol.

The buccal smears, consisting of scrapings taken from the mucosa of the cheeks by means of a clean tongue depressor, were prepared in the same fashion as the vaginal smears.

The smears of the urinary sediment were prepared from specimens of urine to which several cubic centimeters of 95 per cent alcohol were immediately added to prevent disintegration of the epithelial cells. Within three hours, the urine was centrifuged, the supernatant liquid discarded, and the sediment thinly spread on a slide by means of a wire loop. Fixation was immediate to prevent drying.

The staining technique described by Shorr,[11] a single differential trichromatic staining solution, was used for all smears.

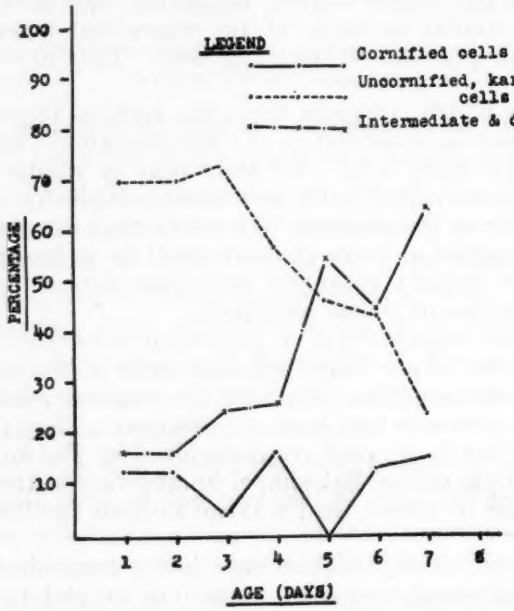

Fig. 1.—Percentage of cell types obtained from the vaginas of thirteen newborn female infants.

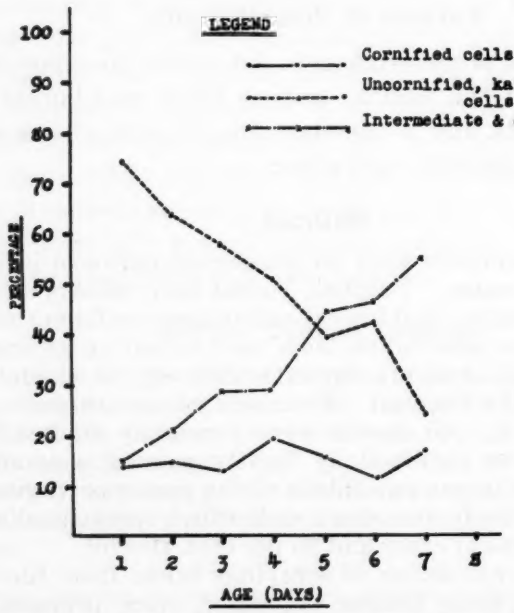

Fig. 2.—Relationship of cell types found in the urinary sediment of twenty-five newborn infants.

Results

The daily variations in the cytology of the vaginal, urinary, and buccal components from the age of 1 day to 7 days in the 25 newborn infants studied are summarized in Table I. The interpretation of the variations is, however, facilitated by graphs (Figs. 1 to 4).

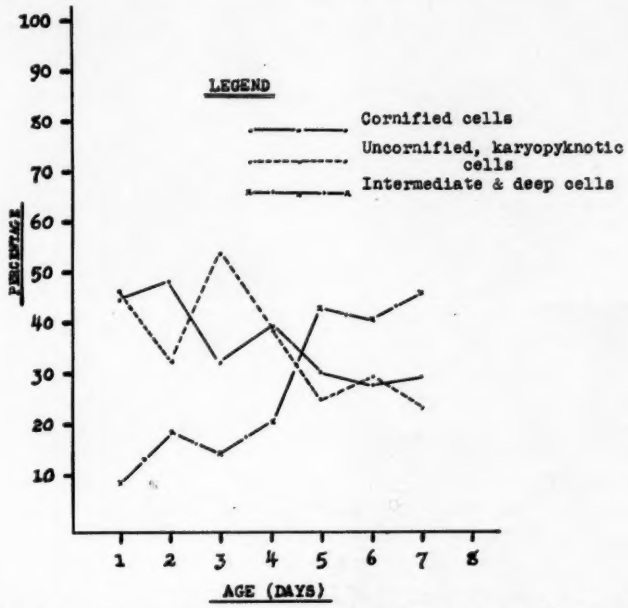

Fig. 3.—Comparison of cell types obtained from buccal mucous membrane of twenty-five newborn infants.

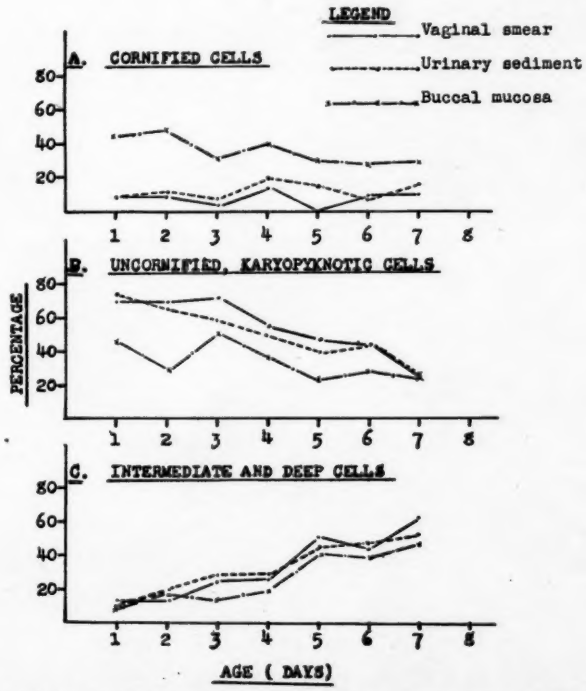

Fig. 4.—Comparison of the percentage of similar type cells as found in the vaginal smear, urinary sediment, and buccal mucosa of twenty-five newborn infants.

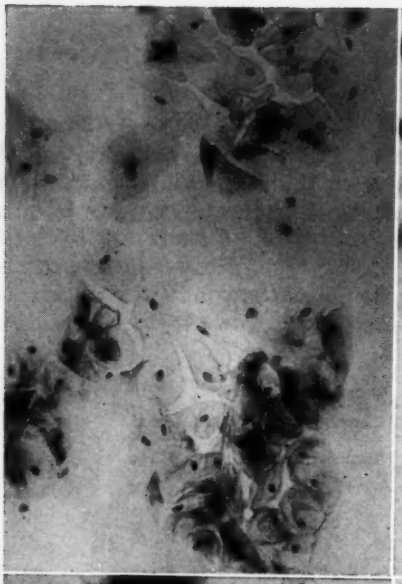

Fig. 5.

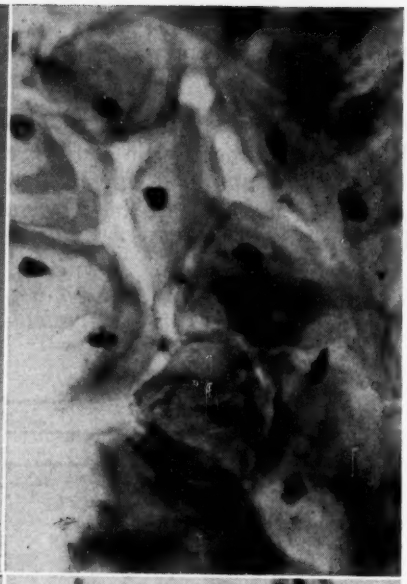

Fig. 5 *A*.

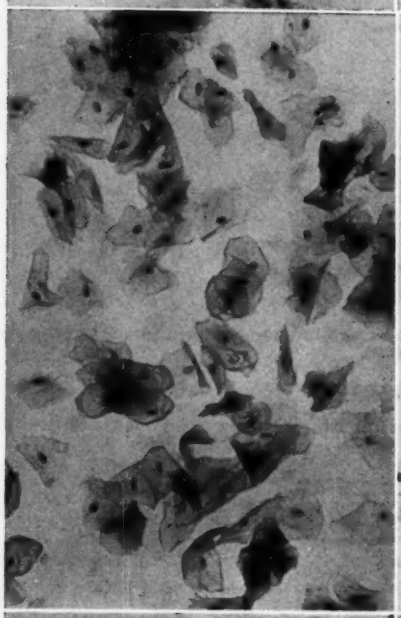

Fig. 6

Fig. 7.

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Fig. 8 *A*.

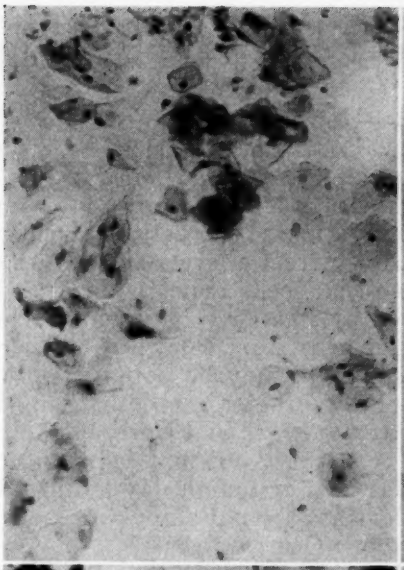

Fig. 9.

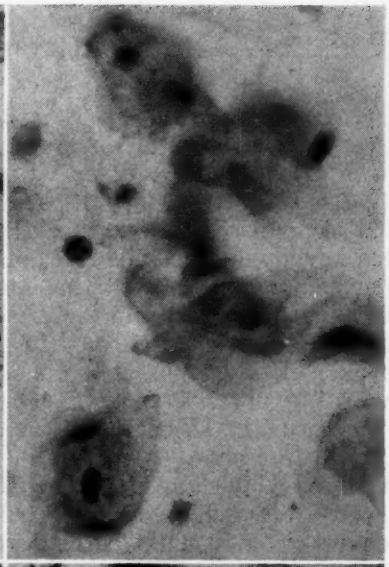

Fig. 9 *A*.

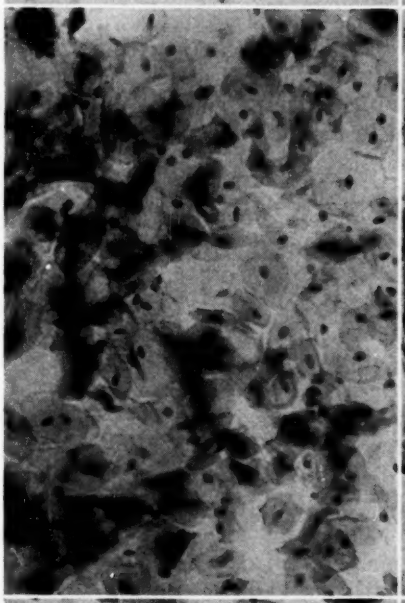

Fig. 10.

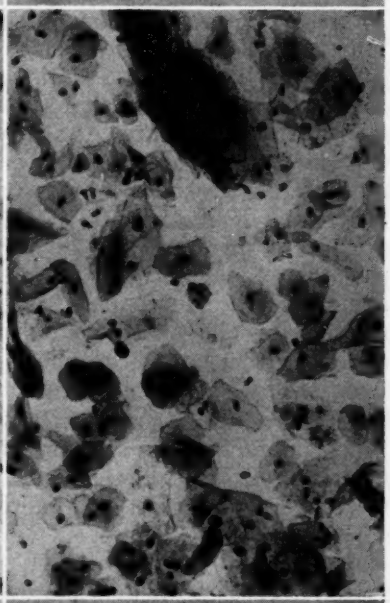

Fig. 11.

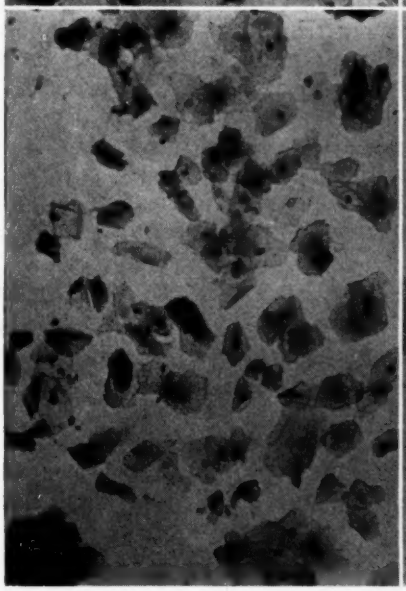

Fig. 12.

Fig. 12 *A*.

A. Cytology of the Vaginal Smears.—It will be noted from Fig. 1 that the cornified cells of the vaginal smears remain at about the same level during the first week of life (13 per cent on day 1 and 14 per cent on day 7). Only an occasional granular cell is noted. However, a marked variation occurs in the uncornified elements of the vaginal smear. The large, polygonal, homogeneous uncornified karyopyknotic cells fall abruptly from a level of 70 per cent on day 1 to 23 per cent on day 7. At the same time, cells from the intermediate and deep layers of the vagina, characterized by smaller cells having larger nuclei with a well-differentiated chromatin net, rise from a level of 17 per cent on day 1 to a level of 68 per cent on day 7. It may be noted that the deeper elements of the mucosa show a relatively greater increase than the intermediate constituents. The transition is quite gradual until the third to the fifth day when the changes become more striking. It may be noted in passing that leukocytes which appear about the third or fourth day tend to disappear by the seventh day. The leukocytic elements are not a striking feature of the vaginal cellular constituents of the newborn (Figs. 5 to 8).

B. Cytology of the Urinary Sediment.—A striking parallelism is noted between the constituents of the smear of the urinary sediment and the elements of the vaginal smear. This is quite evident in comparing Figs. 1 and 2. The cornified elements of the urinary epithelium remain at approximately the same level for the seven days of study, varying from 13 per cent on day 1 to 17 per cent on day 7 and reaching a high level of only 20 per cent on day 4. Few granular cells are noted. Once again, however, there is a striking shift in the uncornified derivatives. The uncornified karyopyknotic cells fall sharply from 73 per cent on day 1 to 28 per cent on day 7, while the intermediate and deep elements rise abruptly from a level of 14 per cent to 55 per cent during the same period. Here, too, it may be noted that the deep elements of the desquamated cells, characterized by small round cells with small amounts of blue-violet cytoplasm and large nuclei, show a relatively greater increase than the intermediate constituents (Figs. 9 to 12).

C. Cytology of the Buccal Mucous Membrane.—The cytologic variations of the oral mucosa show a less striking similarity to the vaginal and urinary constituents; nevertheless parallelism is still quite evident (Fig. 3). The cornified cells show a wider variation and are present in larger numbers than in any of the foregoing smears. The levels vary from 44 per cent on day 1 to 30 per cent on day 7, reaching a high of 49 per cent on day 2. Once again, granular elements are rare. The uncornified constituents show similar variation to that of the epithelia of the vagina and urinary tract, but the variations and level are less marked. The uncornified karyopyknotic cells drop from an initial level of 47 per cent on day 1 to 23 per cent on day 7 with a high of 53 per cent on day 3, while the intermediate and deep elements rise from 9 per cent to 47 per cent during the same time. There are relatively fewer deep cells than noted in the components of the vagina and urinary tract (Figs. 13 to 16).

It should be noted that no differences occurred in the buccal and urinary smears between the male and female infants in all of the smears studied.

Comment

As pointed out in the preceding paragraphs, a striking correlation was noted between the epithelial constituents of the vagina, oral mucosa, and urinary sediment in the 25 newborn infants studied. This parallelism, involving the three major components of the exfoliated cells, is depicted graphically in Fig. 4.

These observations show that the vaginal epithelium is the most sensitive to the decreasing titer of estrogenic hormone in the newborn, the urinary

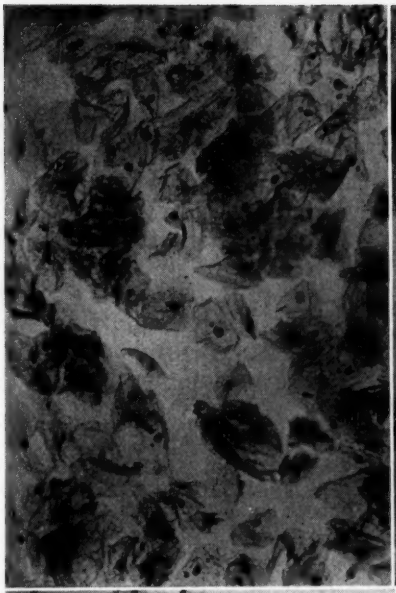

Fig. 13.

Fig. 13 *A*.

Fig. 14.

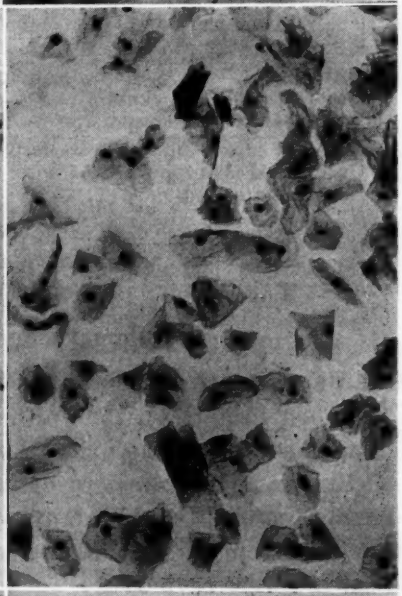

Fig. 15.

Fig. 16.

Fig. 16 *A*.

tract epithelium is only slightly less responsive, and the oral mucosa the least reactive. The striking similarity in behavior of the vaginal and urinary epithelia may be explained by the fact that the urethra is a derivative of the urogenital sinus, possessing the capacity to react rapidly to estrogens.[4]

It should be noted that there is still a low-to-moderate level of estrogen at 7 days of age, and that this may be the explanation for the relatively large number of intermediate cells observed. If this study had been extended to 14 days of age, one might logically expect a smear predominantly of deep cells. The relative lack of the granular elements in the cornified cells may be explained by the fact that the estrogenic level is never sufficiently high to cause a significant number of such cells to appear.

TABLE I. DAILY VARIATIONS IN THE CYTOLOGY OF THE VAGINAL, URINARY, AND BUCCAL COMPONENTS OF 25 NEWBORN INFANTS (13 MALES AND 12 FEMALES), IN THE FIRST WEEK OF LIFE

TYPE OF SMEAR	CELL TYPE (%)	AGE IN DAYS						
		1	2	3	4	5	6	7 AND 8
Vaginal	Cornified	13	13	4	17	0	13	14
	Uncornified karyopyknotic	70	70	72	57	46	43	23
	Intermediate and deep	17	17	24	26	54	44	63
Urinary	Cornified	13	15	12	20	16	11	17
	Uncornified karyopyknotic	73	64	59	51	40	43	28
	Intermediate and deep	14	21	29	29	44	46	55
Buccal	Cornified	44	49	32	40	31	29	30
	Uncornified karyopyknotic	47	32	53	39	26	30	23
	Intermediate and deep	9	19	15	21	43	41	47

Summary and Conclusions

1. In an attempt to correlate the effect of the falling estrogenic hormone level in newborn infants on the epithelium of the vagina, urinary tract, and oral mucosa, smears from the urinary sediment, buccal mucous membrane, and vagina of 12 female infants and smears from the urinary tract and buccal mucous membrane of 13 male infants were studied. Specimens were obtained every other day from the first to the seventh day after delivery from each infant; 244 smears were reviewed.

2. The constituents of each smear were classified into (a) cornified cells, (b) uncornified karyopyknotic cells, and (c) intermediate and deep cells.

3. A striking parallelism was observed between all three sets of epithelium, characterized by (a) only slight variation in cornified cells, (b) sharp decrease in uncornified karyopyknotic constituents, and (c) marked increase in intermediate and deep elements, the latter showing the greatest change. No difference in buccal or urinary smears was noted between the male and female infants.

4. The similarity of the cytologic variations between the vaginal and urinary constituents is more striking than between the oral mucosa and the other constituents.

5. It is apparent from the present study that the vaginal epithelium best reflects the changing estrogenic level, that the urinary sediment follows it closely, and that the oral mucosa is least responsive.

The author wishes to thank Dr. S. Leon Israel and Dr. David R. Meranze for their gracious encouragement, and the Department of Research for the enabling Grant-in-Aid.

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Discussion

DR. A. E. RAKOFF.—I believe that Dr. Rosen deserves to be congratulated for the very excellent study he has so carefully executed. I think his choice of the newborn as an experimental subject in whom to carry out his experiment, namely, comparison of the epithelium from three points, was a good one. Except for the newborn, there is no other physiological state in which estrogen reaches such a high level and then falls so rapidly, so that there is an excellent opportunity to evaluate changes at the height of estrogen concentration and during and after its rapid fall in the newborn. As a matter of fact, the drop in hormone level in the newborn is even more rapid than we used to think it was. Studies we recently carried out with Dr. Sosnowski indicate that the high estrogen level at the end of pregnancy falls to very low levels within eight hours. This rapid drop of estrogens, however, does not necessarily mean that the subject is entirely deprived of estrogen, because considerable estrogen is stored in the liver and then slowly excreted in the bile, with small amounts entering the systemic circulation, which is probably why the estrogen effect continues to fall over a period of one week.

This study depicts not only a change in the estrogen level but a fall in the progesterone level as well. This is the reason why the level of cornified cells is only 10 to 20 per cent at delivery. If estrogen had been present alone, the cornified cells would have approached 100 per cent.

The findings indicating similarity of the cytologic changes in the urinary tract and vaginal tract have been noted before. The appearance of some of the cells in the urine of pregnant women is so characteristic that at one time it was suggested as a pregnancy test.

The changes in the urinary tract raise another question from an embryologic standpoint: namely, the fact that the vaginal epithelium responds so well to estrogen has been used as evidence indicating that it is of Müllerian origin rather than arising from the urogenital sinus. The finding that the urinary tract is almost as sensitive to estrogen as the vaginal epithelium invalidates this argument.

The changes in the buccal membrane are interesting. Some years ago we made a study with a dental group of the mouths of pregnant women. The changes were not nearly so striking as they are in the vagina. We did not get as good a correlation as did Dr. Rosen in the newborn. We did note, however, marked hyperkeratosis with marked cornification of buccal epithelium in occasional pregnant women.

A TWENTY-YEAR STUDY OF RADIOLOGICAL TREATMENT OF CANCER OF THE CERVIX AT THE MONTREAL GENERAL AND ROYAL VICTORIA HOSPITALS*

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THE treatment of carcinoma of the cervix today is in a state of flux; one clinic favors surgery because it claims that radiological treatment is at a standstill, while another maintains that best results are still to be attained by careful and individualized treatment with x-ray and radium therapy. No one can predict the final role of either surgery or radium and it is likely that the last word in treatment will come from neither radiation nor surgery, but from more recent methods of therapy as the cobalt bomb or indeed from some new, as yet unknown method. It is, however, only by evaluation of the apparent five-year recoveries that one can evolve policies as to the best methods of treatment. For this reason it was decided to present the results of twenty years of radiological treatment of carcinoma of the cervix cases treated at the Royal Victoria and Montreal General Hospitals betwen the years 1927 and 1946, inclusive.

From 1920 to 1925, when most clinics turned from the surgical to the radiological treatment of cancer, to the present time, progressive increase in the number of these cases salvaged by radiation therapy has been noted. Though this improvement has not been startling, it nevertheless has been steady.

Heyman[1, 2] reports a 22.3 per cent five-year survival rate for the years 1914 to 1933; whereas his five-year cure rate for 1934 to 1943 is 38 per cent, an increase of 15.7 per cent. A still further 7 per cent improvement is noted in his figures for 1944 and 1945 when 45.2 per cent of the patients treated are alive today. This improvement Heyman attributes to "individualization of treatment"; that is, with increased experience, the radiotherapist has been able to apply radium and administer x-ray therapy more efficiently and to modify the technique as required. Hunt[3] reports a 20.5 per cent salvage for the years 1931 to 1936, whereas from 1937 to 1941, 42.1 per cent of the patients were alive after five years, an increased salvage of nearly 20 per cent.

The twenty years under review also show a steady improvement in the five-year results in both Montreal hospitals. The cases have been divided for comparison into two ten-year periods, 1927 to 1936, and 1937 to 1946. The series comprises twelve hundred cases of invasive cancer of the cervix, 506 patients who were treated at the Montreal General Hospital, and 694 at the Royal Victoria Maternity Clinic. The method of treatment in both institutions was very similar. In Stage I and II and most Stage III cases, the treat-

*Read before the Royal College of Physicians and Surgeons of Canada, Toronto, Ont., Oct. 4, 1952.

ment consisted of two radium applications given at ten-day intervals, followed by a series of deep x-ray therapy treatments. An intrauterine tandem of two 25 mg. tubes of radium (screened in 2 mm. brass and 3 mm. rubber) with three 25 mg. tubes in the vagina, one placed against the cervix, and one in each lateral fornix, was used as the basic treatment. This treatment was often modified to suit the individual patient. Sometimes the applicator used was a Clarke's tube, a Swansberg tube, straight tubes, Stockholm boxes, or ovoids depending on the size of the tumor and the width of the vagina. General anesthesia was always used as an aid to satisfactory application of the radium. Great care was taken in packing the vagina to be sure the lateral tubes were as far apart as possible—and that the bladder and rectum were adequately protected by increasing their distance from the radium. An indwelling catheter was inserted and the bladder emptied at frequent intervals. The dose at the first treatment was 2,500 mg. hr., whereas at the second treatment 2,000 to 3,500 mg. hr. was given, making a total dose varying from 4,500 to 6,000 mg. hr.

For the sake of convenience, we have usually given both radium treatments before the deep x-ray therapy; and we now believe that the parametria can be more effectively irradiated by placing the tubes in the noncontracted vagina; and by tighter packing greater screenage is possible for the bladder and rectum. In Stage IV cases, x-ray was given as a palliative measure to lessen discharge and bleeding. In the few Stage IV cases which showed an unexpected response, radium was applied cautiously at the completion of the deep roentgen therapy. Interstitial radium has not been used in any of these cases for we have felt that the added hazards of hemorrhage and infection offset its value. Cases complicated by infection were usually treated by x-ray first followed by radium.

X-ray therapy was administered through four ports of 150 sq.cm. each. Two hundred kilovolts were utilized, filtered through 0.5 c.c. of copper, to give a total dose of 1,750 to 2,250 r as measured in air, or 1,800 to 2,300 r against the lateral pelvic wall which is calculated to be 5 cm. lateral to the internal os of the cervix. Lateral ports and intravaginal therapy were tried in a few cases but abandoned. The central zone, irradiated by radium, was protected by a midline lead strip from further excessive exposure.

Result of Treatment

Twelve hundred cases of invasive carcinoma of the uterine cervix treated between 1927 and 1946 show an over-all five-year salvage of 36 per cent. Table I shows the cases divided into two ten-year periods, and gives the percentage of five-year recoveries in each.

TABLE I. RADIATION THERAPY RESULTS

YEARS	NO. PATIENTS	5 YEAR CURES	
		NO.	PER CENT
1927-1936	557	173	31
1937-1946	643	260	40
Total	1,200	433	36

Tables II and III show the results of radiation in the two series, when the cases are divided into four stages.

TABLE II. RADIATION RESULTS, 1927-1936

STAGE	PATIENTS		5 YEAR CURES
	NO.	PER CENT	PER CENT
I	64	11.4	71.4
II	96	17.2	51.0
III	270	48.4	25.1
IV	127	22.8	9.4
Total	557		31.4

TABLE III. RADIATION RESULTS, 1937-1946

STAGE	PATIENTS		5 YEAR CURES
	NO.	PER CENT	PER CENT
I	73	11.3	73.3
II	168	26.1	60.1
III	283	44	35.3
IV	119	18.5	4.1
Total	643		40.4

When we compare the two series, 9 per cent more patients are alive and well five years following radiation in the second series. This increased salvage is distributed over the first three stages but is most marked in Stages II and III as will be seen in Table IV.

TABLE IV. COMPARISON OF FIVE-YEAR CURES

STAGE	FIVE-YEAR CURES	
	1927-1936	1937-1946
I	71.4%	73.3%
II	51.0%	60.1%
III	25.1%	35.3%
IV	9.4%	4.1%

Since the percentage of early and late cases influences prognosis, the number of Stage I and II and of Stage III and IV cases are compared in Table V. The number of early cases (Stages I and II) was nearly 9 per cent higher in the 1937-1946 series.

TABLE V. EARLY AND LATE CASES

YEAR	STAGES I AND II		STAGES III AND IV	
	NO.	PER CENT	NO.	PER CENT
1927-1936	159	28.5	397	70.1
1937-1946	241	37.4	402	62.5

This increase in the number of Stage I and II cases is undoubtedly a contributing factor in the improved survival rate. Table V also shows that the educational campaign carried on by the Red Cross Society and the medical profession concerning cancer is showing results. However, we feel with others that greater care in the application of radium and of deep x-ray therapy, adjustment of the treatment to the individual patient so that radiation is more evenly distributed combined with more blood transfusions, bed rest when necessary, diet, and good nursing care have also increased the number of cures. The improvement in Stage II and III cases seen from 1937 to 1946 can be

explained only by greater destruction of metastatic lymph glands. The radium dose applied to the cervix has either remained the same or been decreased in the latter series whereas the remainder of the pelvis has received heavier radiation from both vaginal radium and x-ray therapy.

Complications following radiation are often mentioned by those who favor surgery. But here, too, the number of serious complications has greatly decreased with the less empirical treatment in the latter series of cases. Cystitis, bladder fibrosis with decrease in bladder capacity, vesicovaginal fistulas; proctitis, rectal ulcers, fistulas, and intestinal obstruction have all occurred. As a rule, fistulas and obstruction have been due to persistent disease. McCormick[4] has shown that 23 per cent of 72 patients treated prior to 1939 showed complications from treatment, whereas of 216 patients treated between 1939 and 1948 only 6.5 per cent showed any complications, and in only 1 per cent was the injury really severe.

The reports of Heyman, McKelvey, Hunt, and Schmitz, as well as our own figures, show that the radiological treatment of carcinoma of the cervix is not at a standstill. That still further progress is probable is shown by the work of physicists and radiologists being done on radioactive gold and cobalt; the more accurate measurement of roentgen units delivered to various points in the pelvis; and the more powerful x-ray machines and cobalt bombs which are being built. Brown[5] has shown that 5,000 to 6,000 r is the minimal cancerocidal dose to the lateral pelvic wall. In a series of cases with metastatic glands the above dose of radium and x-ray was given by Brown so as to radiate the pelvic wall adequately. At laparotomy six weeks later all the radiosensitive tumors showed no malignant glands. Thus it is not by increasing the dose of gamma rays to the cervix but rather by distributing the dose over the entire pelvic area, that greater success will be attained. Allen of St. Louis working with radioactive gold is also obtaining accurate estimation of the amount of radiation picked up by the lymph glands. These more modern concepts of radiation therapy will undoubtedly add much in the days ahead to a more effective treatment of carcinoma of the cervix.

In spite of these advances, radiation therapy still has its limitations. Twenty-five per cent of Stage I cases, possibly including many with lymph node involvement, are not cured by radiation today, the so-called radioresistant cases. Recurrence following radiation does not respond to further roentgen or radium therapy. Some cancers even in the early invasive stage seem to be so malignant that in spite of any known form of therapy, radiation or surgical, they recur. These cases form a problem which has caused some to turn again to surgery. If we could select the resistant cases, at the start (and attempts are being made to do so), these cases might be salvaged by careful surgery. Combined radiation and surgery may also be an answer in a few selected cases. However, owing to the magnitude of the operation, and the technical difficulties involved, the surgical removal of the carcinomatous cervix should still remain an experimental project to be undertaken only by those particularly trained for the work. Anything less than very radical removal of all the pelvic organs and glands will prove worse than useless. Hence in invasive carcinoma of the uterine cervix, the keystone of treatment today must continue to be radiation.

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PRIMARY CARCINOMA OF THE VAGINA

A Report of Forty-six Cases

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PRIMARY carcinoma of the vagina is a rare disease, usually insidious in its onset and in the past has had a relatively poor prognosis. More recent reports do not reflect the pessimism of the early writers and many improvements in therapeutic procedures have been suggested.

Baldwin[1] reviewed the records at the University of Michigan Hospital from 1902 to 1931 and found only 10 true primary carcinomas of the vagina. From 1931 through 1950, 55 patients with this diagnosis have been processed in our Gynecology Tumor Conference. Ten of these cases were not included in this study for the following reasons: 2 were seen once and for consultation only; the remaining 8 were eliminated because the primary lesion could not be *positively* placed in the vagina. One case was seen in March, 1951, making a total of 46 cases here reported conforming to the definition set up by the League of Nations Health Organization[2] in 1939. In each case a confirmation of the diagnosis was made by histopathological examination of excised portions of the tumor. Follow-up with every patient was maintained after treatment through periodic hospital examinations, reports from the family physician and the Social Service Department.

Incidence

Livingstone,[3] who has published the largest single series of primary vaginal carcinomas (110 cases), reports that they represented only 0.25 per cent of all the admissions to Memorial Hospital, New York City, within the period considered and only 2 per cent of the primary carcinomas of the female genital tract. Emmert[4] reported 30 cases, 1.9 per cent, among 1,546 female genital cancers and Way's[5] 44 cases represented an incidence of 1.6 per cent. Williams[6] found only 2 cases in the Boston City Hospital from 1906 to 1930. Taussig[7] in 1935 reported the incidence to be 2.7 per cent.

At the University of Michigan Hospital, the relative incidence of the 46 cases used in this study is 1.5 per cent. For every case of primary vaginal carcinoma there were 44 carcinomas of the cervix, 9 of the endometrium, 5 of the ovary, and 3 of the vulva (Table I).

Age

Novak[8] believes the most common age for this disease is between 35 and 50 years. Ewing[9] places it as low as 30 to 40. In Livingstone's series the average age was 55 years. The average age incidence in Way's New Castle series was 54 years with the youngest 24 and the oldest 73. In our series the extremes were 15 and 83 with average age of 64 (Fig. 1). A review of the literature revealed only 7 cases in women under 20 years of age. Because of the patient's youth, the following case is reported in detail.

TABLE I. DISTRIBUTION OF 2,988 MALIGNANCIES OF THE FEMALE GENITAL TRACT STUDIED BY THE GYNECOLOGY TUMOR CONFERENCE (JULY 1, 1931 TO DECEMBER 31, 1950)

DIAGNOSIS	NUMBER OF NEOPLASMS	PERCENTAGE OF ALL NEOPLASMS SEEN
Carcinoma of cervix uteri	1,999	66.9
Carcinoma of endometrium	428	14.3
Carcinoma of uterus (site of origin unknown)	7	0.2
Carcinoma of ovary	230	7.7
Carcinoma of vagina	55	1.8
Carcinoma of vulva	117	3.9
Carcinoma of clitoris	20	0.7
Carcinoma of Fallopian tube	3	0.1
Carcinoma of Bartholin gland	2	0.1
Sarcoma of uterus (cervix or corpus)	36	1.2
Carcinoma and sarcoma of body of uterus	4	0.1
Chorioepithelioma	15	0.5
Pelvic malignancy, unclassified	68	2.3
Sarcoma of vagina	4	0.1
Total	2,988	

(From the *University of Michigan Medical Bulletin*, vol. 17, Oct., 1951.)

Case Report

Miss K. F., aged 15 years, single, entered the University Hospital with the chief complaint of a profuse, foul-smelling, vaginal discharge associated with pain in the perineum. Her menstruation had been regular and normal since the age of 11 years. About one year before admission she noticed an increasing white vaginal discharge with a foul odor, but no intermenstrual bleeding. Four months prior to hospitalization she began to have intermittent pains and she developed a dull ache in the vagina. She gradually lost weight, became fatigued easily, and stayed in bed a great deal of the time. She was seen and treated by her local physician on several occasions, but pelvic examination was not done.

On physical examination the patient appeared thin, pale, and subacutely ill. There was moderate tenderness to palpation in the lower abdomen with a sense of resistance just above the pubis. There were some small lymph nodes palpated in the right groin, but no tenderness was noted. Just within the introitus on the posterior vaginal wall there was a necrotic, ulcerated, bleeding lesion about 3 cm. wide and 7 cm. long. In the lower half of the vagina the growth extended onto the lateral vaginal walls, but became narrow in the upper one-half and was absent at the posterior fornix. The lower portion of the rectovaginal septum was about 1 cm. thick and paravaginal thickening extended to the pelvic walls bilaterally. A biopsy specimen was reported by the pathologist as revealing "far advanced medullary squamous cell carcinoma, Broders' Class IV." A lymph node removed from the right groin showed lymphadenitis but no carcinoma. The patient was treated palliatively with 3,000 mg. hr. of radium and died four months later at her home. No autopsy was obtained.

Race and Parity

There were 43 white women, 2 Negro, and 1 Mexican in the group of 46 seen at the University of Michigan Hospital from 1931 to 1951. All but 2 were married or had been married. Five were nulliparous, 12 had only one child, 15 had two or three children, and 14 had four or more children. Thirty-five patients had ceased to menstruate prior to the onset of the symptoms associated with the vaginal carcinoma. Five of these had an artificial menopause, 3 by surgical procedures, and 2 by x-ray castration. The average age of those who reached the menopause spontaneously was 51 years.

PRIMARY CARCINOMA OF THE VAGINA

A Report of Forty-six Cases

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(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

PRIMARY carcinoma of the vagina is a rare disease, usually insidious in its onset and in the past has had a relatively poor prognosis. More recent reports do not reflect the pessimism of the early writers and many improvements in therapeutic procedures have been suggested.

Baldwin[1] reviewed the records at the University of Michigan Hospital from 1902 to 1931 and found only 10 true primary carcinomas of the vagina. From 1931 through 1950, 55 patients with this diagnosis have been processed in our Gynecology Tumor Conference. Ten of these cases were not included in this study for the following reasons: 2 were seen once and for consultation only; the remaining 8 were eliminated because the primary lesion could not be *positively* placed in the vagina. One case was seen in March, 1951, making a total of 46 cases here reported conforming to the definition set up by the League of Nations Health Organization[2] in 1939. In each case a confirmation of the diagnosis was made by histopathological examination of excised portions of the tumor. Follow-up with every patient was maintained after treatment through periodic hospital examinations, reports from the family physician and the Social Service Department.

Incidence

Livingstone,[3] who has published the largest single series of primary vaginal carcinomas (110 cases), reports that they represented only 0.25 per cent of all the admissions to Memorial Hospital, New York City, within the period considered and only 2 per cent of the primary carcinomas of the female genital tract. Emmert[4] reported 30 cases, 1.9 per cent, among 1,546 female genital cancers and Way's[5] 44 cases represented an incidence of 1.6 per cent. Williams[6] found only 2 cases in the Boston City Hospital from 1906 to 1930. Taussig[7] in 1935 reported the incidence to be 2.7 per cent.

At the University of Michigan Hospital, the relative incidence of the 46 cases used in this study is 1.5 per cent. For every case of primary vaginal carcinoma there were 44 carcinomas of the cervix, 9 of the endometrium, 5 of the ovary, and 3 of the vulva (Table I).

Age

Novak[8] believes the most common age for this disease is between 35 and 50 years. Ewing[9] places it as low as 30 to 40. In Livingstone's series the average age was 55 years. The average age incidence in Way's New Castle series was 54 years with the youngest 24 and the oldest 73. In our series the extremes were 15 and 83 with average age of 64 (Fig. 1). A review of the literature revealed only 7 cases in women under 20 years of age. Because of the patient's youth, the following case is reported in detail.

TABLE I. DISTRIBUTION OF 2,988 MALIGNANCIES OF THE FEMALE GENITAL TRACT STUDIED BY THE GYNECOLOGY TUMOR CONFERENCE (JULY 1, 1931 TO DECEMBER 31, 1950)

DIAGNOSIS	NUMBER OF NEOPLASMS	PERCENTAGE OF ALL NEOPLASMS SEEN
Carcinoma of cervix uteri	1,999	66.9
Carcinoma of endometrium	428	14.3
Carcinoma of uterus (site of origin unknown)	7	0.2
Carcinoma of ovary	230	7.7
Carcinoma of vagina	55	1.8
Carcinoma of vulva	117	3.9
Carcinoma of clitoris	20	0.7
Carcinoma of Fallopian tube	3	0,1
Carcinoma of Bartholin gland	2	0.1
Sarcoma of uterus (cervix or corpus)	36	1.2
Carcinoma and sarcoma of body of uterus	4	0.1
Chorioepithelioma	15	0.5
Pelvic malignancy, unclassified	68	2.3
Sarcoma of vagina	4	0.1
Total	2,988	

(From the *University of Michigan Medical Bulletin*, vol. 17, Oct., 1951.)

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Possible Predisposing Factors

Our attention was attracted to two factors often listed as possible predisposing factors in carcinoma of the vagina: (1) prolonged use of a pessary, and (2) senile vaginitis.

One patient 67 years of age had worn a glass pessary for two and one-half years without removing it. She developed vaginal "spotting" and after several weeks consulted a physician who found it necessary to do a perineotomy to remove the pessary. The vaginitis present at the time of the operation confused the examiner, but a biopsy taken one month later revealed the presence of the carcinoma.

Two other patients had marked senile vaginitis which masked the clinical picture, causing delay in biopsy and diagnosis of the carcinoma. Treatment was delayed five months in one patient and nine months in the other. Only 6 patients (13 per cent) gave a family history of cancer.

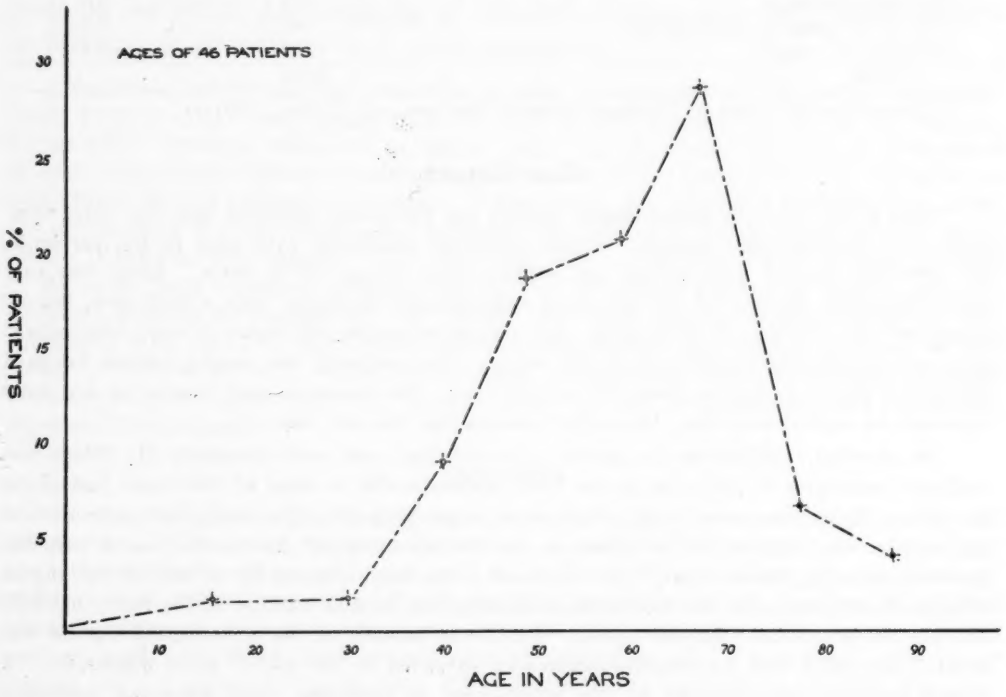

Fig. 1.

Symptoms and Clinical Course

The walls of the vagina are thin and well supplied with a network of blood and lymph vessels which suggests that symptoms might appear early. If this be so the symptoms are apparently overlooked or ignored, for the time wasted in our 46 patients between the onset of symptoms and the first medical consultation averaged 5.7 months. The extremes of this period were two days for one patient and thirty-six months for another. Other writers report a similar period of delay. Moench,[10] 7 months; Livingstone,[3] 9.8 months, and Lehman and Jones,[11] 4.8 months.

The initial symptom of "painless abnormal bleeding" was the first sign noted in 31, or 67 per cent, of our series. In 21 of these there had been rather conspicuous postmenopausal spotting. Seven women noted their first irregular spotting after intercourse and three had spontaneous intermenstrual bleeding.

The delay of more than five and one-half months in seeking medical advice after abnormal vaginal bleeding points to the necessity of continuing the constant and intensive efforts to teach the public to fight cancer with alert suspicion and periodic examination.

Eight patients reported leukorrhea as their initial symptom with 3 describing it as a watery discharge. Three palpated a nodule in the vagina before noting any symptoms; 3 complained of pain in the perineum as the first symptom; and one 80-year-old woman did not suspect she had any serious illness until a metastatic lesion appeared on her left leg associated with pain (Table II).

TABLE II. INITIAL SYMPTOM

SYMPTOM	NO. CASES	PER CENT
Vaginal bleeding	31	67.4
Leukorrhea	8	17.4
Nodule in vagina	3	6.5
Perineal pain	3	6.5
Pain in leg (metastatic)	1	2.2
Total	46	100.0

Location and Size of the Growth

According to many authors the most common location for primary carcinoma of the vagina is the upper one-third of the posterior wall. Twenty-two, or 48 per cent, of the vaginal lesions in our series involved the upper third of the vagina and 21 involved the posterior wall. As Livingstone[3] points out, "The extent of the disease may hopelessly obscure the point from which it developed." Such was the situation in 6 of our cases, where nearly all of the vagina was involved. In 3 others the lesion encircled the vagina leading to an "annular lesion" (Tables III and IV).

TABLE III. LOCATION OF VAGINAL LESION

THIRD OF VAGINA	NO. CASES	PER CENT
Lower	14	30.4
Middle	3	6.5
Upper	22	47.8
All	6	13.1
Undetermined	1	2.2
Total	46	100.0

TABLE IV. LOCATION OF VAGINAL LESION

WALL OF VAGINA	NO. CASES	PER CENT
Anterior	15	32.8
Posterior	16	34.7
Anterior and posterior	5	10.8
Lateral	7	15.2
All	3	6.5
Total	46	100.0

The estimated size of the lesion was given in 45 cases. The smallest was 0.7 cm. in diameter and the largest 7.5 cm. Five patients had more than one lesion. One growth was described as several small nodules close together forming a complete circular lesion in the lower two-thirds of the vagina.

Gross Appearance of the Neoplasm

Healy[12] described in detail the gross appearance of these cancers and divided them into three groups. One group included the spongy, friable, and

highly vascular outgrowths which he found occurred more frequently in older patients known to have had a pre-existent vaginitis. Singh[13] referred to this group as the everting or papillary form. We had 13 cases (28 per cent) that fitted this description. Four of them were pedunculated or polypoid in character.

Healy's second group was described as the infiltrating, circumscribed, resistant tumors which usually acquired an ulcerated surface. Twenty-five, or 54 per cent, of our cases fell into this category.

A third and smaller group includes the annular, constricting forms of carcinoma which make a narrow, rigid tube of the vagina. Only 3 (6.5 per cent) of the 46 cases in this report were of this type. Five cases were not described sufficiently to permit inclusion in any of the three groups. One adenocarcinoma was described as semicystic and the size of a hen's egg.

Extension of the Neoplasm

Forty of the 46 patients had clinical extravaginal extension of the carcinoma at the time of our initial examination. Two of the 6 without apparent extension developed spread after therapy began and did not survive. The other 4 survived more than five years. Some had multiple metastases and others only a single remote deposit. The broad ligaments were found to be infiltrated in 19 cases; the rectovaginal septum in 7; the bladder in 5; the rectum in 4; the inguinal nodes in 3; the vulva in one, and the bony ischium in one. Secondary involvement of the cervix occurred in one patient but there was no question in the mind of the examiner but that the primary lesion was in the vagina.

Distant metastasis to bone was proved by x-ray in 4 cases. To the tibia in 2, the ischium in one, and to vertebrae and skull in one. One patient had roentgenographic evidence of pulmonary metastases and cancer cells in the sputum. Other terminal cases had metastases to the liver, adrenals, brain, and skin, proved by autopsy.

Seven of the 11 patents who survived five years or more had definite extension into surrounding pelvic tissues at the time treatment began. Only 3 in this group had delayed longer than four months after the onset of bleeding before consulting a physician. One delayed eleven months, one twelve, and one fourteen months.

Four of the patients sought medical advice soon after the initial symptoms appeared, but they died of cancer in less than two years. Way[14] suggests that time and size of the lesion are secondary factors in carcinoma spread and that some specific power on the part of the tumor causes some tumors to penetrate the lymphatics easily and quickly. Anaplastic tumors have a greater potentiality for penetrating lymphatics and tend to spread more rapidly than the differentiating ones. He believes that lymphatic spread is, in most cases, by embolus and not by permeation.

Histopathology

In all of the cases in this study the clinical diagnosis was confirmed by histopathologic studies of biopsy material. Forty-three were described by the pathologist as squamous-cell carcinoma and thirty-six were graded according to the degree of anaplasia (Table V and Figs. 2 and 3).

TABLE V. HISTOPATHOLOGIC GRADING OF 36 CASES

GRADE	NO. CASES	PER CENT
I	1	2.8
II	11	30.6
III	19	52.7
IV	5	13.9
Total	36	100.0

Three cases were diagnosed as papilliferous adenocarcinoma of the vagina. Because it was realized that this was a rare tumor, every effort was made to find a primary site, other than the vagina. Sigmoidoscopic, cystoscopic examinations and careful clinical follow-up failed to disprove that these patients had primary adenocarcinoma of the vagina (Fig. 4).

Fig. 2.

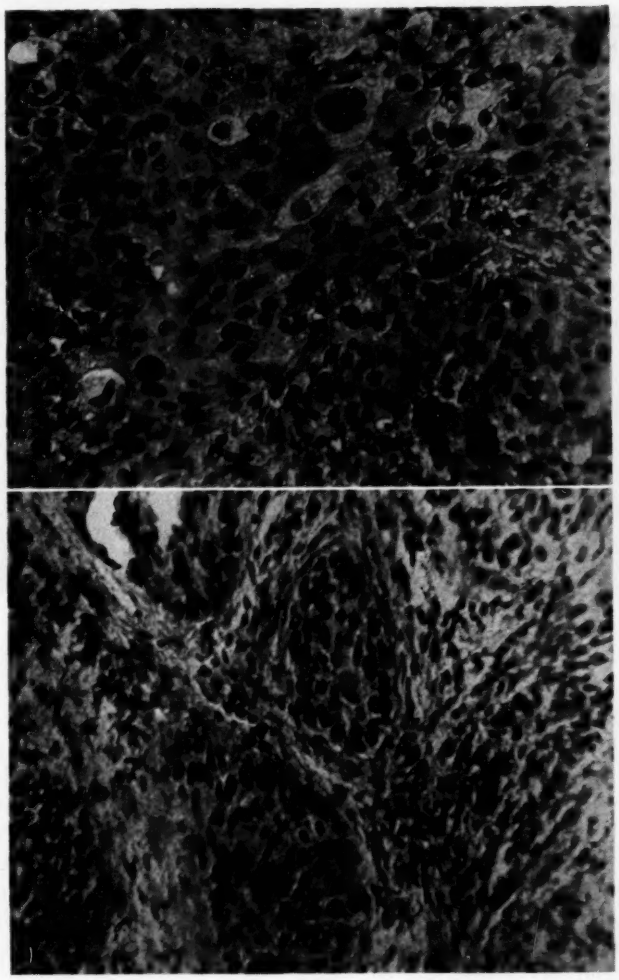

Fig. 3.

Fig. 2.—Primary squamous-cell carcinoma of the vagina, histological Class IV.
Fig. 3.—Primary squamous-cell carcinoma of the vagina, histological Class III.

Some writers on the subject believe that the source of these adenocarcinomas is vestiges of Gartner's duct in the vaginal wall. Others suggest they are from aberrant cervical glands in the fornix. But adenosis of the vagina as described by Bonney and Glendenning[15] in 1910 and more recently by Plaut and Dreyfuss[16] is the most probable antecedent and has been supported by authentic case reports.[14] Plaut and Dreyfuss believe that adenocarcinoma of the vagina, in most instances, originates from glands in the vaginal wall which are not normally present but which come from the Müllerian epithelium which takes part

in the formation of vaginal mucosa. Piper[17] describes a case of adenocarcinoma diffusely spaced in the vaginal epithelium.

Livingstone[3] found 7 primary adenocarcinomas in 110 cases (6.4 per cent), Moench[10] reported 2 in 37 cases (5.4 per cent) and Way[5] 2 in 44 cases (4.5 per cent). Way[14] believes one of his cases was preceded by adenosis of the vagina and the other one arose from a Wolffian remnant because it contained corpora amylacea such as those found in the prostate.

Two out of the 3 patients with adenocarcinoma in our study have survived more than five years without recurrence, but all 4 patients with adenocarcinoma in Livingstone's determinate group died from the disease.

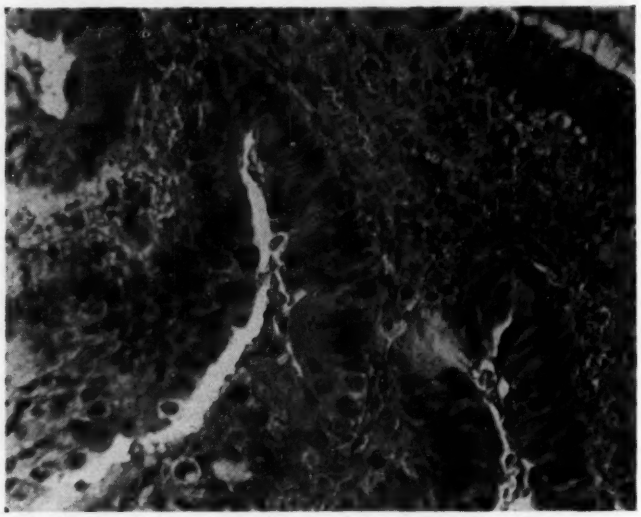

Fig. 4.—Primary adenocarcinoma of the vagina.

Treatment and Results

The history of therapy for carcinoma of the vagina began with Herman[18] in 1886, when he purposely created a vesicovaginal fistula to relieve urinary retention. Ten years later Roberts[19] advocated excision of certain small tumors and after Wertheim[20] described his radical operation for carcinoma of the cervix in 1905 it was used for a few carcinomas involving the upper third of the vagina.

In 1903 Alexander Graham Bell suggested to a physician that radium be used for internal cancer as well as skin cancer. But even after several years of experience with x-ray and radium in the treatment of cancer, Taussig's[7] often-quoted statement appeared in 1935, "We acknowledge our total inability to do anything effective for primary carcinoma of the vagina." The disease is rare and any individual's experience is so limited that he has little chance to work out new ideas of therapy and accumulate sufficient data truly to evaluate his results. Many applicators and techniques of radium and x-ray therapy have been described in the literature but the number of patients in each group was not great enough to be statistically significant.

Courtial[21] at the Paris Radium Institute in 1939 reports the highest five-year survival rate. Ten of 22 patients treated survived five years or more (45.4 per cent). Singh[13] reported a series of 21 patients treated at Sloane Hospital without any five-year survivors.

Livingstone,[3] reporting 110 cases with a complete follow-up on 76, had 8 patients (10.5 per cent) who survived five years or more without evidence of

cancer. Way[5] in 1948 reported 18.2 per cent five-year survivors in 33 cases. Five of 25 treated with radium only survived. Only 7 of his total series[14] of 64 cases were treated solely by surgery. Two of these had purely local excision and survived, while all of those who had radical surgery died in less than five years.

Buschke and Cantril,[22] in 1951, report 5 out of 10 patients surviving more than four years after a full course of x-ray therapy and local radium to the central portion of the lesion.

Table VI shows the methods of therapy used at the University of Michigan Hospital in the 46 cases here presented. The absolute five-year survival among the 40 eligible cases was 11 patients, or 27.5 per cent. Table VII shows the three-year, five-year, and ten-year survival rates.

TABLE VI. TYPE OF THERAPY

TREATMENT	NO. CASES
Radium only	4
X-ray only	6
Radium and x-ray	28
Surgery	
a. Local excision with x-ray and radium	3
b. Local excision with x-ray	1
c. Local excision with radium	2
d. Radical Surgery—hysterectomy, bilateral salpingo-oophorectomy with radium and x-ray	1
Refused therapy	1
Total	46

TABLE VII. ABSOLUTE SURVIVAL RATES

SURVIVAL PERIOD	NUMBER ELIGIBLE	NUMBER ALIVE	PER CENT ALIVE
3 years	42	12	28.5
5 years	40	11	27.5
10 years	27	5	18.5
15 years	14	1	7.1

It is difficult to evaluate statistics regarding therapeutic results. One should know among other things the clinical extent of the disease at the time treatment was begun. Since Courtial[21] has the best five-year survival rates, we used the clinical classification which he arbitrarily set up in order to get a comparison in end results. By definition, Courtial's Stage I is a strictly vaginal lesion, not yet passing beyond the muscular tunica of the vagina, not involving more than one-half of the surface area of either the posterior or anterior vaginal wall, with only slight infiltration; Stage II: a lesion with a surface area extending over more than one-half of the anterior or posterior wall, infiltrating paravaginal soft tissues unilaterally or bilaterally but without demonstrable infiltration into the rectal or bladder mucosa; Stage III: tumors with infiltration and fixation to the pelvic bone or infiltrating mucosa of the urethra, bladder, rectum or involving the vulva.

All of Courtial's patients were treated with either x-ray or radium or a combination of the two while some of our patients had surgery. Table VIII shows the results of therapy in both series plus the stage of extension of the disease when therapy was begun.

The practical significance of this method of presentation is rendered indeterminate by the small group of patients in each subdivision and by the lack of histopathologic confirmation of the diagnosis of extension. But it does re-

emphasize that the small lesions without apparent spread beyond the vaginal walls respond well to therapy.

Livingstone,[3] although using a slightly different clinical classification, obtained only 3 cures in 20 cases (10.7 per cent) in which the disease was presumably limited to the vagina. He obtained 5 cures in 48 cases (10.4 per cent) with clinically suggested spread which further emphasizes the limitations of compared results.

TABLE VIII. COMPARISON OF SURVIVAL RATES

REPORT	CLINICAL STAGE	NO. CASES	5 YEAR SURVIVAL	PER CENT
Courtial	I	3	3	100.0
	II	11	6	54.0
	III	8	1	12.0
Total		22	10	
University of Michigan	I	4	4	100.0
	II	23	7	30.0
	III	13	0	0.0
Total		40	11	

Comment

By comparing the absolute five-year survival rates of carcinoma of the cervix and carcinoma of the vulva with that of primary carcinoma of the vagina, one can readily see there are fewer survivors when the primary lesion is located in the vagina. At the University of Michigan Hospital, the absolute five-year survival rate from 1931 to 1951 for carcinoma of the vagina was 27 per cent (40 cases), and carcinoma of the vulva, 38 per cent (99 cases). The absolute five-year survival rate for carcinoma of the cervix (all stages) based on 89 cases seen in 1945 was 47.2 per cent.[23] Livingstone[3] collected 970 cases of primary carcinoma of the vagina from the literature in 1950 and found an over-all five-year survival rate of 12 per cent.

In reviewing the lymphatic drainage of the vagina, one finds the lower portion is drained through the same channels as those of the vulva and the upper part is similarly identical with that of the cervix. The drainage of the middle third is in both directions, but only 20 per cent of the carcinomas of the vagina in this series involved the middle third.

It seems logical to assume, therefore, that if one treated primary carcinoma of the lower third of the vagina with radical excision and careful dissection of the inguinal lymph nodes as we do carcinoma of the vulva, and carcinoma of the upper third of the vagina as we treat carcinoma of the cervix, the survival rate might improve.

For those that are inoperable, deep x-ray therapy and a centrally located radium application should be made. This may require special vaginal applicators as described by Way[14] or even an individual mold of the vaginal canal so that a perfect applicator for that patient can be made.

Progress in therapy is more likely to be made if patients with this rare disease are funneled into the larger treatment centers. Then enough experience can be gained to evaluate therapeutic procedures more accurately.

Summary

1. Forty-six cases of primary carcinoma of the vagina are reported. They made up 1.5 per cent of nearly 3,000 malignancies of the female genital tract seen at the University of Michigan Hospital from 1931 to 1951.

2. Twenty-eight patients were treated with radium and x-ray, seven with surgery and x-ray or radium, six with x-ray only, four with radium only, and one refused therapy.

3. There were eleven five-year survivors in forty eligible cases, making a 27.5 per cent absolute five-year survival rate. There was no apparent correlation between the degree of anaplasia of the tumors and the five-year survival rate.

4. Some suggestions concerning therapy have been offered.

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LATE RESULTS WITH THE INTERPOSITION OPERATION

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TWENTY-SIX years ago I published my first article[1] on the use of the interposition operation in the treatment of uterine prolapse. It was based on the study of 56 patients, some operated upon by Cullen, the rest by myself. Fifty-six is not a large number, and yet the results obtained and the almost complete absence of complications showed the value of the operation. Today my enthusiasm for the interposition is as great as it was when my first report was made, provided that its use is restricted to carefully selected cases and no important steps are omitted in the operative technique.

Forty-eight of the fifty-six patients in the first series were traced. Forty-five of these forty-eight (94 per cent) stated that the operation completely relieved all their symptoms and on examination it was shown that the prolapse had been entirely corrected. Three women were glad they had been operated on but did not consider the results entirely successful. Only one needed further surgery. She developed a cystocele but not until the eleventh postoperative year.

This one failure provides an opportunity to emphasize that to judge correctly the results obtained in the treatment of uterine prolapse, cystocele, rectocele, or enterocele it is necessary to follow patients many years after their operations. Several types of operative procedures give immediate good results but the aim must be an operation that gives a patient relief not merely for five or even ten years, but for as long as she lives. Not infrequently women go for many years without any return of the uterine prolapse and then, because of atrophy and weakening of the structures, the tissues suddenly give way, as happened eleven years postoperatively in this case.

There were no fatalities in this first series and, which is remarkable, no complications except for one case of severe cystitis which persisted for several months. Today with sulfonamides and antibiotics this would probably have been a matter of weeks or even days instead of months. These patients were all operated upon prior to 1926 but even today these results seem impressive.

Nine years after this first report, Everett[2] published a report on the interposition operation based on sixty-eight cases operated on at the Johns Hopkins Hospital between 1927 and 1931. Sixty-seven patients were discharged as well. One died of pulmonary embolism. Forty-eight of the 67 patients were traced. Forty-six (95 per cent) were relieved of all their symptoms and pelvic examination showed excellent anatomical results. Two cases were classified as failures

because there was a recurrence of the prolapse. However, in neither of these did the prolapse return until five years after the operations and during these five years the patients experienced complete relief from all their symptoms. If one made the mistake of considering as permanently cured all patients well at the end of five years the interposition operation could be said to have been 100 per cent successful.

In 1948 my second article[3] on the interposition was published. The details of that report will be incorporated in this paper which is based on all the interposition operations carried out at the Johns Hopkins Hospital between 1915 and 1952 and on those I performed in any of the Baltimore hospitals including those done at Johns Hopkins. The total number is 332. Fifty-two were my private patients, the remaining 280 were operated on by the other members of the visiting staff and the gynecological residents of the Johns Hopkins.

There were three deaths, but none in the past eight years. One fatality on the seventh postoperative day was due to coronary disease and might have occurred if the patient had not been operated on. The other two were the result of pulmonary emboli. By getting patients out of bed on the day of operation or on the following day the danger of embolism is decreased but not eliminated. In the past ten years the great majority of all my gynecological patients have been ambulated early and during that time only one small embolus was observed from which the patient quickly recovered. Incidentally, it has been my experience that those patients on whom I performed vaginal hysterectomies have objected more to early ambulation than have those who had interposition operations.

The only serious operative accident was the perforation of the bladder in one case. The opening was immediately closed and the patient had no postoperative difficulty. In one of the early cases the body of the uterus was so badly traumatized in being delivered into the vagina that a partial fundectomy was added to the interposition operation which actually turned the procedure into a modified Richardson composite operation.

The nonfatal complications consisted of sixteen infections of the bladder and two instances of thrombophlebitis. Fourteen of the bladder infections cleared up promptly. Two persisted for two months. Now that the patients are ambulated early and given Gantrisin prophylactically the number of urinary infections is less than it was ten years ago.

The two cases of thrombophlebitis were mild and the patients were having very little trouble when they were discharged from the hospital. These two women had not been ambulated early. Possibly if they had the thrombophlebitis might not have developed.

In only one patient did any postoperative bleeding occur and it was not profuse. It came from the anterior wall of the vagina and was easily controlled. It is my impression that postoperative hemorrhage is observed more often after vaginal hysterectomies than after interposition operations.

In three cases the body of the uterus had been previously removed by abdominal hysterectomy and in later years the cervical stump had prolapsed. The operation performed on these three women consisted of amputating the

lower part of the remaining cervix and interposing the upper portion under the bladder following the same principles as are used in interposition operations. The results were good in all three cases.

The cervix was not amputated in many of the early cases in the series. Now it is taught that amputation should always be done. Hence we find that while the cervix was removed in only 174 of the entire series of 332 cases, it was in 41 of the most recent 42.

On microscopic examination the great majority of the amputated cervices showed infection. Twenty-two showed hyperkeratosis; fourteen squamous metaplasia; and one a very early squamous-cell carcinoma. This patient was operated on twenty years ago. As the patient was then 61 years of age and the amputation had been made sufficiently high to give considerable margin above the malignant lesion, no further treatment was advised. She was examined thirteen years later with absolutely negative findings.

There were no instances of carcinoma in situ reported. This may seem strange but carcinoma is rarely seen in the cervix of a prolapsed uterus. Its rarity is such that individual cases are sometimes reported in the literature. Why with the constant trauma to which the prolapsed cervix is exposed malignant changes do not develop more often is just another one of the things not understood about cancer.

It is important to question all women who have had any vaginal plastic operations about postoperative dyspareunia, for it may occur after any of them. However, it must be remembered that many women beyond 50 who have not been operated on complain of painful sexual relations. When this is due to surgery it is more often caused by a perineorrhaphy which is too tight than by a vaginal hysterectomy or interposition operation. If it is present the daily use for three weeks of an estrogenic ointment or cream applied by the patient through a syringe to the vagina and manually to the vulva often overcomes this difficulty. Actually, many of the patients on whom we have performed interpositions in the past twenty years have been of such an age that their sex life had come to an end before the prolapse was corrected.

Of the fifty-two patients on whom I operated, two were over 75 years of age and eleven between 65 and 75. Twenty-nine were between 55 and 65 and eight between 45 and 55. Only two were under 45.

The oldest patient was an 82-year-old woman whose life was made miserable by a complete uterine prolapse with marked ulceration of the cervix. Careful medical examination by an internist showed her to be in surprisingly good condition. She withstood the operation which lasted for thirty-five minutes very satisfactorily and is now quite happy and remarkably active for her age of 84. The two youngest patients were both 42 years of age. One had had a bilateral salpingectomy previously and the other was a widow who was absolutely sure she would not remarry.

There is no doubt that speed in surgery is not of the importance that it was thirty years ago due to improved anesthesia and to the ease with which transfusions can be given. Nevertheless, in choosing between procedures to be carried out on elderly women, a saving of twenty to thirty minutes of operative

time is of value. The average time taken to complete the last thirty-one interpositions was fifty-six minutes. Eleven of these were completed in forty-five minutes or less and two performed on elderly women where there was a definite indication to hurry in thirty-five minutes. Possibly the Le Fort operation can be done more rapidly than an interposition operation by those who have performed many Le Forts, but in the few instance in which I have used this operation it has taken me as long to do as does an interposition.

One woman whose operation I classify as a failure merely notices that when she stands she can feel the cervix at the vaginal orifice. Three other women were well for ten years and then had to have a second operation, one for prolapse of the uterus; a second for cystocele; and a third for rectocele. These three must be classified as failures. For a plastic operation to be considered a success it must hold the tissues in their places indefinitely.

Another case classified as a failure about which I feel very bad was that of an enormous woman with very limited mentality and a complete prolapse. The abdominal examination was negative except for the marked obesity. The interposition operation was carried out without difficulty. The ovaries, as is customary, were palpated and inspected. The patient left the hospital twelve days after the operation and also left the city. Four months later she returned to the hospital and was found to have bilateral ovarian carcinoma. A laparotomy was performed but she died shortly afterward.

Much has been written about the danger of cancer developing in the uterine fundus left at the interposition operation. In the series of 332 cases this did not occur once. On the other hand one hears very little about the danger of ovarian carcinoma when the ovaries are left in and yet it does occasionally occur. I have in many cases removed the ovaries through the vagina, but in some instances have found it a little difficult to do. I am not advocating the routine removal of ovaries with either vaginal hysterectomies, composite or interposition operations. This unfortunate case is mentioned simply because I believe it does make us think.

Two of my private patients cannot be traced. One, as just stated, died of ovarian cancer. The remaining forty-nine have been followed postoperatively and feel that the operation helped them greatly. Sixteen years have elapsed since one of them was operated on at the age of 66. At 82 she is still active. Twenty-five have survived the operation for more than ten years, thirty-five for more than five years. These few personal figures indicate that the interposition operation holds the tissues in the proper place many years postoperatively. In the entire series, as has been stated, the operation was successful in 277 of the 289 patients traced, or in 96 per cent of the cases.

Comment

These results convince me that the interposition operation has served me well. Nevertheless, I realize that today the operation is seldom used. Even in the hands of my colleagues at the Johns Hopkins Hospital the vaginal hysterectomy, the Manchester operation, and the Richardson composite operation are employed much more frequently. What may seem even more remarkable is

that the house staff of the Hospital for the Women of Maryland usually treats cases of uterine prolapse by vaginal hysterectomy. In permitting this, a policy is followed which has been in existence at the Women's Hospital for many years, namely, that the chief does not force all of his ideas on the house staff so long as he is satisfied that they are doing competent work.

However, as stated at the beginning of this paper, my enthusiasm for the interposition operation is still as great as it was twenty-six years ago and I consider the recent loss of popularity of the procedure unjustified. So long as it is never employed when contraindicated and no essential steps in the operative procedure are omitted, the interposition is a useful and safe operation.

The interposition operation is contraindicated under the following conditions: first, when it is possible for pregnancy to occur after the operation, second, in those women who are having profuse menstrual periods at the time of the menopause whether or not the uterus contains fibroids. In such cases the uterus should be removed. Although among those who do interposition operations there are some who feel that the procedure should be limited to first- and second-degree prolapse, I have used it successfully in many cases of complete procidentia.

The steps which are sometimes omitted in performing the interposition operation and which in my opinion should never be omitted are the following: The cervix should always be amputated. This not only does away with the possibility of cervical malignancy developing in the future but definitely increases the chances for permanent correction of the prolapse. Next, it is essential that the bladder be sufficiently mobilized, especially laterally. It should be freely separated from its vaginal and uterine attachments and the bladder pillars cut. To quote from Phaneuf,[4] "The bladder thus becomes an abdominal organ, it rests on the superior and posterior surfaces of the uterus and it lies smoothly and not in folds over the interposed uterus." Care should also be taken not to suture the cut edge of the uterovesical fold too far back on the posterior surface of the uterus. For several years I did not sew the peritoneum back to the uterus at all. I usually do so now although there were no complications in the cases in which this step was omitted.

The top sutures of those interposing the uterus should be introduced high up into the subpubic structures. If this is not done, it is possible for the interposed uterus to work its way from under the symphysis and while still remaining anteflexed to prolapse. I have never seen this happen but Dannreuther[5] reported several cases in which this occurred. I like to bring the pubocervical ligaments together in the midline under the interposed uterus before tying the fixation sutures. This step may not be necessary but it does seem to give added support.

What are some of the criticisms today by those who do not believe in the operation? To speak of the difficulties which may occur if the patient becomes pregnant is to criticize not the operation but the operator for not knowing the contraindications. Some gynecologists have stated that it would be very difficult to remove the uterus that had been interposed and in which malignancy later developed. Dannreuther reported such a case and stated that the opera-

tion presented no technical difficulties. J. Mason Hundley in a personal communication told me of a patient on whom an interposition operation was performed and whose curettings twenty-four hours later showed fundal carcinoma. He merely cut the fixation sutures from below and then easily performed an abdominal hysterectomy. There have doubtless been other instances of this complication but these are the only two of which I have found any record. Certainly it should occur rarely for, as has already been stated, the cervix should be amputated routinely and the operation not employed for women with profuse bleeding at the time of the menopause. Moreover, an interposition should always be preceded by a uterine curettage and if the curettings are profuse or suggest malignancy or hyperplasia, either a corrective operation should be postponed until a microscopic report is obtained or a vaginal hysterectomy carried out.

Bladder symptoms and complications may of course develop after any operation to correct uterine prolapse, but I have observed them less frequently after an interposition operation than after a vaginal hysterectomy. However, I am certain that in the past ten years the number of urinary complications in my private patients following all types of vaginal surgery has been lessened by getting the patients out of bed early. This certainly decreases the number of catheterizations needed. I feel that one should guard against giving these patients too much intravenous fluid with the resulting overdistention of the bladder. If nausea has ceased on the second day I usually discontinue intravenous therapy and rely on what the patient can take by mouth, and protect against infection by giving 1 Gm. of Gantrisin every six hours for three days. Rarely are retention catheters necessary.

Now, having presented our results with the interposition operation and having endeavored to point out how the complications which some claim are likely to develop can be avoided, are there any features of the interposition operation which give it a special appeal even if the results are not better than with other procedures used for uterine prolapse? The answer is yes. The procedure is technically simple and can be carried out more easily and usually more rapidly than either a vaginal hysterectomy or a Richardson composite operation.

Another important factor which does not today receive sufficient attention in deciding between operations is blood loss. This is usually much less with the interposition operation than with other operations used to correct uterine prolapse. In fact, in the last twenty-five interposition operations included in this report, in only two were transfusions given and in one of these there was an operation on the neck in addition to the gynecological procedure. I have observed many vaginal hysterectomies in Baltimore and elsewhere and in many, if not the majority of them, one or several pints of blood were given and were definitely needed.

We have all come to look too lightly on the giving of transfusions. No one could possibly question their lifesaving value when needed but they are two-edged swords. This was clearly brought out in an article by Timothy B. Talbot[6] published in October, 1950, in *Surgery, Gynecology and Obstetrics.* To quote directly from his paper, "Many serious hazards do exist and blood transfusions

are both potentially and actually a dangerous undertaking. It is unfortunate that there are such risks, but it is essential that the clinician recognize their existence.'' Talbot then emphasizes that there are other complications such as homologous serum jaundice and so forth, besides the hemolytic and pyrogenic transfusion reactions with which all are familiar. This article is most illuminating.

Conclusion

On the basis of the foregoing, I am still using the interposition operation to correct large cystoceles, first- and second-degree uterine prolapse, and often third-degree or complete procidentia. The complications have been few and the mortality low. The operation is easy to perform and usually accompanied with little blood loss.

In closing I should like to quote from an article by Baer[7] read before the American Gynecological Society on June 2, 1937. This speaker, after discussing the operations used for uterine prolapse and pointing out that his results were better with the interposition operation than with the vaginal hysterectomy, made the following comment: ''The technique of the interposition operation must be properly carried out. The patients must be well selected and the result then is satisfactory. I am particularly glad that the society accepted this re-birth of the interposition operation because I think it was being slowly shelved and I am glad to have had some small part in calling it to your attention.'' My feeling today about the interposition operation is the same as was Baer's in 1937. However, I am not very hopeful that there will be any rebirth of the operation. The trend toward vaginal hysterectomy in cases with and without prolapse has become very strong, possibly unjustifiably so. I still believe in the interposition operation and will continue to use it, feeling certain it has a very definite place among gynecological procedures.

The late J. M. T. Finney once said something like this, ''Keep informed as to what others are doing. Try new procedures when they seem promising, but if you continue to perform the operations which in your hands have given you the best results you will be best serving your patients.'' I am certain that I have no group of gynecological patients on whom I have operated who are more grateful and more satisfied than those on whom the interposition operation was performed.

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Medical Arts Building

Department of Case Reports
New Instruments, Etc.

CERVICAL PREGNANCY

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IT IS probable that many early cases of cervical pregnancy are overlooked and are treated as ordinary missed abortions. Careful scrutiny will demonstrate a placenta which is firmly attached and breaks up into fragments on attempted removal. The following is a case report of an early cervical pregnancy.

Mrs. M. K., a 25-year-old nullipara, was admitted to Huron Road Hospital Jan. 4, 1950, complaining of severe vaginal bleeding. Her past personal history was essentially without event with the exception of a curettage and cauterization of the cervix for cervical erosion in 1948. At this admission her menstrual period was two weeks late. On Dec. 30, 1949, she began to have vaginal spotting which persisted and was accompanied by crampy pains over the lower abdomen. Approximately four to five hours prior to admission vaginal hemorrhage became profuse. On admission to the hospital she was in a state of impending shock with a thready soft pulse and a blood pressure of 80/50. The red blood count was 3,320,000 with 56 per cent hemoglobin.

Fig. 1.—Drawing of gross appearance of cervical pregnancy.

The physical examination revealed no significant findings other than marked pallor of the skin and the previously described signs of acute blood loss.

She was transfused with 500 c.c. of whole blood, immediately taken to surgery, and pelvic examination was performed. The cervix appeared enlarged to twice its normal size and the anterior lip bulged with a bluish, somewhat cystic-appearing mass approximately 3 cm. in diameter which overlapped the external os.

Curettage was performed and decidualike tissue was obtained. Bleeding was demonstrated from the medial surface of the anterior lip. The cystic mass on the anterior lip was excised with a small wedge of the cervical lip to which the growth was firmly attached. The raw bleeding base was then cauterized. Following this procedure the patient's condition appeared satisfactory and the postoperative course was without event.

Histological examination of the specimen obtained at surgery showed in one area a mass of placental tissue attached to the surface and extending into the wall of the cervix. There were numerous large and medium-sized villi with a few masses of decidual cells at the periphery of the pregnancy (Fig. 2).

Fig. 2.—Placental tissue attached to the wall of the cervix.

This case seems to fulfill the criteria laid down by Rubin,[1] and at approximately one month's gestation is the earliest cervical pregnancy yet reported. The presence of decidua supports the contention that the endocervix may undergo decidual change, thus permitting nidation of the fertilized ovum in the cervical canal.

To reconstruct the morphologic sequence of the course of this pregnancy it seems plausible to assume that the fertilized ovum entered the cervix and became embedded on the anterior lip. The ovisac then developed in the wall of the cervix with expansion toward and erosion of the mucosa, terminating by rupture into the cervical canal.

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SECONDARY ABDOMINAL-WALL PREGNANCY

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RUPTURED ectopic pregnancies occur rather frequently, and their sites of rupture are varied. An ectopic pregnancy with rupture into the abdominal wall is extremely rare and in reviewing the literature we have been unable to find a report of a similar case. However, in 1923, Streeter reported a case, "a subcutaneous implantation of an ovum." An embryo was recovered under the skin in a woman who had previously had a ventrofixation operation. No evidence of a tube was found at operation.

The occurrence of a pregnancy in a Fallopian tube which was suspended in the abdominal wall at a previous operation for retroversion and its subsequent rupture into the surrounding rectus muscle is a bizarre incident. The gestation was entirely limited to that portion of the tube that was brought up through the abdominal wall instead of the round ligament. The remainder of the tube as well as the tube on the opposite side were apparently normal. A hysterosalpingogram performed postoperatively revealed the fact that the other tube was patent and in its normal position. This was clearly seen on the lateral films. Simple wide excision of the involved portion of the tube with the evacuation of the products of conception and blood clots produced a cure in this case.

The patient was a 22-year-old nulligravida admitted to the hospital on Oct. 14, 1951, with the chief complaint of dysmenorrhea since puberty and a lump in the right lower quadrant of about three years' duration. The mass varied in size during this time, becoming larger and more painful at each period. However, during the past few months, it failed to recede and instead grew larger and more painful. On some occasions walking became quite difficult because of it. Her periods were regular, occurred every 28 days, and lasted four days, until two and one-half months before admission, when she had her last normal menstrual period. She missed one period and then at the time of her expected second period she had what she thought was an unusually heavy period, lasting eight days with the passage of tissue. During these past two months, the patient lost 7 pounds in weight and noticed that the mass in the right lower quadrant of the abdomen became much larger and more painful. There was no nausea or vomiting. There was some enlargement of the breast. In 1949, she had had a Gilliam suspension.

On admission, the physical examination revealed the patient to be in good general health. The temperature was 99.8° F. and the pulse 88. She was a fairly well-nourished, somewhat pale individual. The breasts were slightly enlarged and tender. The heart and lungs were normal. In the abdomen there was a well-healed suprapubic midline scar from a previous operation. The abdomen was flat and soft. In the right lower quadrant was a 4 cm. blue-tinted, elevated, firm, tender, globular mass just under the skin in the anterior abdominal wall. Vaginal examination revealed a soft cervix with slight tenderness on motion. The uterus was anteverted, not enlarged, freely movable, and in no way connected with the abdominal wall mass. There was no vaginal bleeding. The cul-de-sac was free. The adnexa were palpable but not enlarged. Bimanual palpation added nothing to the findings.

Laboratory examination showed a negative urine. The hemoglobin was 14 Gm., white count 10,300 with 81 polymorphonuclear leukocytes and 7 staff cells. The frog pregnancy test was negative.

A preoperative diagnosis of endometriosis of the abdominal wall, following previous uterine suspension, was made. In addition, it was thought that she had a recent complete abortion.

At operation, the previous midline scar was excised and the peritoneal cavity entered. On inspection the pelvic organs appeared normal. A primary focus for the suspected abdominal wall endometriosis was carefully sought for, but none was found. A presacral neurectomy was performed.

Another incision, directly over the mass in the right lower quadrant was made, exposing a large amount of dark-red clotted blood and some necrosis of the right rectus muscle and overlying fascia. Running through this area was a fibrosed band of tissue that appeared to be the round ligament. Owing to the large amount of blood and necrosis, exact tissue landmarks could not be made out clearly. The blood clot, knuckle of fibrous tissue, some muscle and fascia were excised. All devitalized tissue was resected. The exposed end of the excised knuckled fibrous band was resutured to the rectus muscle, lower down. The gap in the rectus muscle and overlying fascia was closed with some difficulty by interrupted sutures.

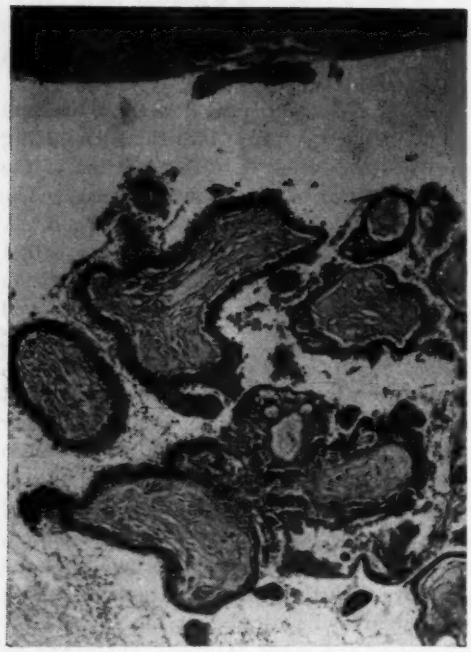

Fig. 1.

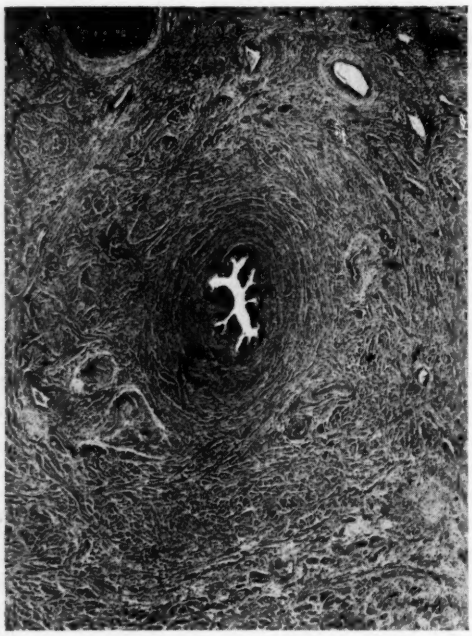

Fig. 2.

Fig. 1.—Section of blood clot showing normal chorionic villi.
Fig. 2.—Fibrous band removed at operation showing portion of a Fallopian tube with markedly hypertrophied muscular wall.

The patient made an uneventful recovery; both incisions healed by primary union. The pathologic report showed blood clot, placental tissue, and marked fibrosis and inflammation of the Fallopian tube (Figs. 1 and 2).

Follow-up observations indicate that the periods have been occurring regularly every 28 days, lasting 4 days, and with absolutely no pain. She has gained about 8 pounds in weight. A hysterogram shows the right tube patent up to the point of operation and the left tube normal in outline and position and completely patent.

Summary

This patient conceived in the portion of the right tube brought up through the abdominal wall in a Gilliam suspension three years before. This tubal gestation ruptured into the abdominal wall. Simple partial salpingectomy, and removal of the products of conception resulted in a cure.

At present she is in the third month of an intrauterine pregnancy.

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TWO SUCCESSIVE ABDOMINAL PREGNANCIES ASSOCIATED WITH UTERUS BICORNIS UNICOLLIS

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THE following case is deemed worth reporting not only on account of the unusual occurrence of two successive abdominal pregnancies, but also because of the presence of a genital anomaly, uterus bicornis unicollis.

The patient, a white woman, aged 24 years at the time of the second laparotomy, had only these two pregnancies. Past history revealed a normal menstrual history and no episode of pelvic disease.

We are indebted to Dr. Herbert White of St. Augustine, Fla., for the details concerning her first pregnancy. Her last menstrual period began Feb. 6, 1949. Pregnancy apparently progressed normally without bleeding or unusual abdominal pain until Oct. 7, 1949, when there was sudden onset of abdominal pain and cessation of fetal movements, followed by slight vaginal bleeding and moderate tenderness of the abdomen. Three days after the onset of pain the breasts became excessively engorged. A diagnosis of abdominal pregnancy was made by Dr. White, on consultation with the patient's physician, and was supported by the roentgen-ray findings.

Surgery was delayed until Nov. 13, 1949 (37 days after fetal death). At laparotomy a 4 pound, 13 ounce, macerated fetus was found lying free in the abdomen except for adhesions between the head and the anterior abdominal wall. The placenta was found attached to the right side of the uterus, the right adnexa, and the right lateral wall and floor of the pelvis. It was easily removed without significant bleeding. The abdomen was closed without drainage and the postoperative course was uneventful.

The second pregnancy dated from a last menstrual flow beginning Nov. 16, 1950. The first two trimesters were again uneventful, without bleeding or pain. On June 23, 1951, there occurred sudden severe pain in the abdomen associated with convulsive movements of the fetus, soon followed by cessation of activity. The patient was aware of a change in the contour of the abdomen, the prominence of the lower abdomen being replaced by a more general but less prominent distention. The abdominal tenderness subsided slowly and on the third day after the onset of the illness the breasts became extremely tense and tender. She was first seen by us on June 27, 1951, on which day she was admitted to Emory University Hospital.

Examination showed her general condition to be satisfactory, temperature 100.4° F., the breasts tensely engorged, and the abdomen moderately distended and tender. There was no evidence of free fluid in the abdomen. A firm mass estimated to be 8 cm. in diameter was felt in the lower left quadrant extending halfway to the level of the umbilicus. A separate softer, tender mass was felt on the right, extending from the pelvis to within 5 cm. of the right costal border. The cervix was in normal position, fairly soft, and could not be traced into either mass. The pelvis was quite tender. No fetal outline or heart sounds could be recognized.

A presumptive diagnosis of abdominal pregnancy was made. Supporting this diagnosis, the roentgen-ray findings included transverse presentation of a fetus lying high above the pelvis and chiefly to the right of the midline, and absence of the outline of the fundus. The hemoglobin was found to be 10.5 Gm. and it was considered advisable to transfuse with 500 c.c. of whole blood. The patient was kept in bed and given injections of penicillin for four days.

Distention and tenderness gradually subsided. During this time slight vaginal bleeding began and persisted for one week. No decidual tissue was noted in the discharge. She was released from the hospital on the tenth day, afebrile and free of pain.

According to plan she was readmitted one month later for surgery. Hysterograms were taken but could not be clearly interpreted until the operative findings were available. Fetal position had changed since the first roentgen-ray film, so that the head lay in the right flank instead of in front of the lumbar spine.

Laparotomy was performed on Aug. 8, 1951, 46 days after fetal death. A 1 pound, 14 ounce, macerated male fetus, 35 cm. in length, was found within a collapsed, nonadherent amniotic sac in the right lower abdomen. The sac still contained a small amount of turbid fluid. There was no evidence of old or recent intra-abdominal bleeding. After removal of the fetus, the placenta was found attached to the structures of the floor and right lateral wall of the pelvis, covering the right adnexa, the bladder, a small portion of the sigmoid colon, and extending slightly onto the anterior abdominal wall. It was easily removed, bleeding from the placental site being insignificant.

An anomalous condition of the uterus was then apparent. There were two uterine corpora, entirely separate down to the cervix, with a tube and ovary attached to the lateral portion of each corpus. The left adnexa seemed normal except for thin adhesions to the posterior pelvic wall. The right tube was edematous and enlarged, apparently due to its involvement in the placental bed. The right ovary was cystic and about 4 cm. in diameter, but required no surgery. The abdomen was closed without drainage and the patient was discharged from the hospital on the seventh postoperative day, after a normal convalescence.

Comment

1. The relatively normal tubes, the similarity in location and attachments of the placenta, and the uneventful and parallel courses of these two successive pregnancies suggest the possibility of primary abdominal pregnancy, since there were no episodes early in pregnancy to suggest tubal abortion or rupture.

2. The anomalous condition of the uterus would seem only coincidental to the extrauterine location of the pregnancies.

3. The abdominal crisis which occurred in each pregnancy was presumably due to spontaneous rupture of the amniotic sac. The relation of this event to fetal death, which occurred at about the same time, is obscure since there was no evidence of disturbance of the placental attachment.

4. The marked engorgement of the breasts, which followed the abdominal crisis in each instance, is of particular interest. Intrauterine fetal death rarely results in breast engorgement. Ware and Main[1] have pointed out that lactation does not occur when the placenta is left in situ at the time of removal of an extrauterine fetus. This has been confirmed by Gardner and Middlebrooks.[2] The accepted explanation is that the placenta continues to secrete estrogen and progesterone which hold the lactation hormone of the pituitary gland in abeyance.[2, 3]

The apparent contradiction in this case may possibly be explained by the flooding of the system with estrogen as amniotic fluid was absorbed through the peritoneum, followed by excretion and rapid decline in the blood level of this hormone, resulting in the initiation of lactation in much the same manner as if the placenta had been removed.

5. Delay in laparotomy in this case made possible removal of the placenta with almost no blood loss. Had laparotomy been performed when the diagnosis was made, and the placenta left in situ, the possibility of residual adnexal pathology would probably have been greater. It must be admitted that, had there been more contact of the placenta with the intestines, infection of the placenta and sac and peritonitis might have occurred. These are some of the considerations involved in the pros and cons of delayed operation.

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MENSTRUATION, PREGNANCY, AND CHILDBIRTH AFTER OPERATION FOR APLASIA OF VAGINA

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VARIED anomalies occur in the female reproductive tract. Cases of congenital absence of vagina are not infrequently encountered. Counseller[1] alone cites 76 cases in a period from 1936 to 1946. A smaller number were reported in which a functioning uterus is present. To date, only three published case reports of vaginal aplasia have appeared in which pregnancy followed surgery. Counseller states that operations for this condition were performed as far back as 1892 when Sneguireff used a rectal transplant to form a vagina. Other operations[2, 3] were devised using different parts of the bowel for transplants, but have since been discarded. Reconstruction of the vagina based on the use of labial[4, 5] and thigh[6, 7] grafts has also been done in the past. In 1938 McIndoe and Banister[8] decided to use a free skin graft for epithelization with a vulcanite mold kept in place 3 to 6 months. Previously, contraction had been the cause of most of the unsuccessful results. At about the same time, Wharton[9] decided to use a balsa mold after dissection, without any skin graft. This is based on the principle that the vaginal epithelium will grow over raw surfaces.

The cases of Whittemore[11] and Wagner,[12] in which pregnancy followed surgery, were alike in that there was evidence of vaginal bleeding before surgery was performed and, in the latter case, delivery of the infant was accomplished per vaginam. Baer[13] noted in his case report that primary amenorrhea existed, and at the time of surgery no definite cervix was found. Two other cases[8, 14] have been reported in which cyclic menstrual bleeding after surgery occurred but in these no pregnancies followed. The case described herein exhibited menstruation and pregnancy followed after surgery. It afforded opportunity to review the cases published earlier and to add ours to this group.

Case Report.—P. P., a 20-year-old white nulligravida, was first seen in February, 1950, with complaint of having had no menstrual periods. She had been married 7 months. The couple seemed well adjusted in their marital life and desired offspring.

Physical Examination: The patient's weight was 133 pounds; height, 63 inches; blood pressure 120/70; pulse, 100 per minute; respirations 24 per minute.

Her general appearance was that of a well-developed woman. Both breasts were small and dome shaped, still retaining some subareolar fat.

The vulva was covered with long hair presenting in distribution a male escutcheon. There was marked hypertrophy of the nymphae which covered completely the vestibule of the vagina. Upon separation of these, a well-developed clitoris was palpated and in the vestibule the only opening present was the urethral meatus. In the mucosa no opening was present where the vaginal introitus would be encountered. Beyond the posterior commissure were the perineal body and anal opening.

On rectoabdominal palpation, a firm, narrow mass was felt to be the cervix and body of uterus. When the finger in the rectum was brought forward toward the vestibular mucosa, no distention or discoloration was noted.

Clinical Course: The patient was placed on thyroid therapy and was re-examined at frequent intervals before operation. She was instructed to carry out a regime of gradual dilatations according to the technique suggested by Te Linde. The basal body temperature was recorded and noted for several months. Four months prior to operation obvious changes in the physical findings were noted. The breasts were enlarged. On rectoabdominal examinations a mass was felt which increased in size up to the time of the operation.

Operation: Surgical correction of the anomaly of the vagina was undertaken on April 17, 1951. An exploratory laparotomy was first performed. The findings revealed presence of a uterus with its attached adnexa. The organ appeared normal in size and contour, presenting a fundus and cervix; the tube and ovary on each side were normal. There was a slight bulge over the peritoneal bladder reflection which, on palpation, revealed presence of a distended cystic mass situated subperitoneally. This mass measured 6 cm. in diameter and contained the portio of the cervix. Intra-abdominally no procedure was performed. The abdomen was closed in the usual manner.

Perineal approach for construction of an artificial vagina was undertaken. A transverse incision was made in the mucosa of the vestibule midway between the urethral meatus and posterior commissure. The mucosa was dissected free to the periphery. The subadjacent tissue was divided by sharp and blunt dissection for a distance of 10 cm. until the distended mass was reached. The mass was incised and a large amount of inspissated dark blood escaped. The cervix was palpated high within this cavity. The lining of the cyst wall resembled vaginal mucosa. The cut edges of the cyst were brought down through the artificial opening and were anchored by a double row of interrupted sutures to the opening in the vestibule. A continuity was thus established between the internal genitals and the newly formed orifice. A glass test tube covered with rubber tissue, measuring 2½ cm. in diameter and about 12 cm. in length, was inserted into this orifice to maintain patency and to act as a drain.

Course in Hospital: The patient had an afebrile course postoperatively. The covered glass-tube drain remained in place and there was a pitch-black tenacious discharge for several days. She was discharged in good condition 7 days after the operation.

Follow-up: The patient was seen immediately postoperatively at weekly intervals. Gradual dilations of the newly formed vaginal introitus were made at these visits. She was advised to resume marital life four weeks following her operation. Penetration was actually experienced.

After the first bloody discharge which was evacuated at the time of operation (April 17, 1951), and which drained for several days after, no staining appeared. Subsequently, a menstrual period was exhibited on May 19, 1951, which lasted 4 to 5 days and was of moderate flow. Vaginal bleeding recurred on June 29, 1951. However, the latter episode was of only 2 days' duration and scanty in amount. In these respects, it was unlike the period which was first experienced immediately after operation. No menstrual bleeding recurred after this and pregnancy followed. This was confirmed by a biological test (***Rana pipiens***).

Ante Partum, Delivery, and Post Partum: Her expected date of confinement was estimated as Feb. 26, 1952. Throughout the prenatal period she gained 15 pounds; urinalysis remained negative; blood pressure ranged from 110/70 to 120/90.

The patient was admitted to the hospital on Jan. 30, 1952, with ruptured membranes and mild irregular uterine contractions. A low cervical cesarean section was performed shortly after admission. A living female child, weighing 5 pounds, 11 ounces, was delivered. Mother and baby were discharged in good condition on the ninth postoperative day.

Examinations made eight weeks and seventeen weeks post partum, respectively, showed normal involution with complete recovery. The periods were re-established, the last two having occurred April 2 to 9, 1952, and May 15 to 18, 1952. The vulval parts remained intact, and the newly formed introitus admitted a gloved finger. On bimanual examination, the uterus was anteriorly placed, freely movable, and involuted. The cervix was inspected and found in satisfactory condition. The basal body temperature was recorded after periods were re-established and revealed a biphasic trend.

Laboratory Findings: The laboratory findings before operation were as follows: The basal metabolic rate ranged from minus 5 per cent to minus 7 per cent. The hemoglobin was 14.2 Gm., red blood cells 5.05 million, white blood cells 10,500 with a differential count of 62 per cent polymorphonuclear neutrophils, 30 per cent lymphocytes, 4 per cent monocytes, 4 per cent eosinophils. Serum cholesterol was 200 mg., glucose 85 mg., urea nitrogen 8 mg., and uric acid 2.9 mg. Prothrombin time (modified Quick's method) was 24 seconds, equivalent to 72 per cent of the norm. Wassermann test was negative, blood was type O, Rh

positive. Urinalysis was negative for albumin and dextrose and revealed 5 to 7 white blood cells per high-power field.

Semen (ejaculate specimen) volume was 2.8 c.c., viscosity and color normal. Count was 128 million per cubic centimeter and the total number of spermatozoa was 358 million. The motility percentage was 62 per cent three hours after emission and the total number of active spermatozoa was estimated at 222 million (motility count with Locke's solution). Determinations of the percentage of active spermatozoa by the hanging drop method were 95 per cent after two hours, 90 per cent after four hours, 60 per cent after six hours and eight hours. There were 89 per cent oval forms of spermatozoa.

After vaginal operation the laboratory findings showed the basal metabolic rate to be plus 1 per cent. The hemoglobin 14.0 Gm., red blood cells 4.98 million, white blood cells 8,000 with a differential count of 58 per cent polymorphonuclear neutrophils, 35 per cent lymphocytes, 4 per cent monocytes, 3 per cent eosinophils. Serum cholesterol was 200 mg., glucose 100 mg., urea nitrogen 8 mg., and uric acid 2.9 mg. Prothrombin time was 16 seconds, equivalent to 100 per cent of norm.

Comment

There is an embryological cause for the occurrence of the varied anomalies of the female reproductive tract. Origin of the imperfections in the vagina is related to two primary sources—anlage from both urogenital sinus and Müllerian ducts. Imperforate hymen is the simplest of these maldevelopments and is related to the former. Vaginal aplasia, as in our case, follows as a result of improper embryonic development from both primary sources. Anomalies of different origin which are present in other systems are frequently found in association with those of the reproductive tract. In Counseller's series, 35 cases were also studied for urinary anomalies and 17 were found to have both.

The inference was made that puberty had not been reached, completely, when the patient was first seen. Occult menstruation had begun later—apparently after thyroid therapy was instituted. Subsequently, a cystic mass was discovered which seemed to increase in size. With the change in the pelvic findings, the presence of a functioning uterus was suspected.

The functional capacity of the female partner depended upon the degree of maldevelopment of the remainder of the reproductive organs. Before construction of a vagina was undertaken, a laparotomy was performed to confirm the presence of a uterus with adnexa. An appraisal of function was to be carried out, subsequently. Semen studies revealed a status of high fertility in the male partner. Correction of vaginal aplasia removed an obstruction to demonstration of functional capacity, namely, menstruation and pregnancy.

Summary

A case of congenital absence of vagina is presented in which the menstrual periods were exhibited and pregnancy and childbirth ensued after operation.

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PREGNANCY FOLLOWING SUBTOTAL HYSTERECTOMY

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THIS 33-year-old white woman, para ii, gravida ii, entered the White Memorial Hospital on April 26, 1948, with the following complaints. For one year she had had dysuria, a weight gain of 25 pounds, pigmented areas on the face, and hoarseness of the voice. The abdomen had been enlarging for six weeks, and for a period of one month she had noticed swelling of the feet, pain in the breasts, and pain in the right lower abdomen. Her past history showed that she had been married for eleven years, and had two children who were now ages 8 and 10. In 1944 she had a subtotal hysterectomy. From this time until the present illness she had felt well and had no menstrual periods or any menopausal symptoms.

Physical examination revealed a middle-aged woman in no distress. Her temperature was 98.8° F. and blood pressure 115/65. Examination of the skin showed some patchy pigmentation of the forehead and sides of the face. The breasts were slightly tender with no abnormal pigmentation. The lower part of the abdomen contained a tense abdominal mass extending upward from the symphysis for 22 cm. This mass appeared to occupy the left side of the abdomen more than it did the right. On pelvic examination the vagina was found to be very long so that the cervix could be palpated only slightly as it was very high in the pelvis. The external os was slightly softened. Superior to the cervix a mass 15 by 20 cm., slightly fluctuant in character, could be felt. This mass appeared to be more on the left side of the abdomen. The diagnosis of an ovarian cyst was made.

An exploratory operation was done and revealed the presence of an intrauterine pregnancy. The uterus appeared to be smooth, the size of a four to four and one-half months' pregnancy. No scars from previous surgery could be found. The abdominal incision was closed without any further exploration, it being assumed that the patient had such a high subtotal hysterectomy previously that enough endometrium remained to sustain this pregnancy.

The patient had an uneventful course until the third postoperative day, at which time quite severe uterine bleeding began. After administering blood by transfusion it was decided to terminate this pregnancy. A course of Pitocin, given by hypodermic injection in 1 unit doses, did not cause any uterine contractions. More blood was given by transfusion, and the patient observed for two days with very little additional bleeding. Since some vaginal spotting still continued, a vaginal examination was done which occasioned the loss of some additional blood. The patient was again given a transfusion and another laparotomy done, at which time the lower part of the uterus remaining was removed. Following this the patient made an uneventful recovery and was dismissed from the hospital eight days later. Since this time the patient has been examined on two occasions, and each time her course has been satisfactory and she has had no complaints.

Comment.—In the few cases of pregnancy following subtotal hysterectomy that have been reported, most of the patients had some menstrual bleeding prior to the cervical pregnancy and following the previous surgery. The absence of any vaginal bleeding following the subtotal hysterectomy in this patient, and the onset of symptoms one year prior to hospitalization led to the diagnosis of a pelvic tumor that had probably been in existence for a year or more. The diagnosis of an ovarian cyst was made, because the tumor was tense and had some fluctuation. It was assumed that rapid growth of the cyst caused the abdominal enlargement six weeks prior to admission.

In retrospect, attention should have been paid to the pigmentation of the face and to the tenderness of the breasts. At the time of the exploratory laparotomy a very normal-appearing pregnant uterus of an estimated four to four and one-half months' duration, with no visible uterine scar, led to the conclusion that a fundectomy or very high amputation of the uterus had been done, so that continuance of the pregnancy might be possible.

In view of the fact that there are no authenticated cases of the survival of a fetus following a vaginal delivery after a previous subtotal hysterectomy, it would have been better for this patient to have had a hysterectomy at the time of the first exploratory operation, since this would not have necessitated the second laparotomy. Termination of the pregnancy through the vagina, by the use of Pitocin to initiate labor, was impossible without danger of much hemorrhage because the contractile portion of the uterus was missing. Presence of the placenta previa over the cervix was not unusual because at the time of implantation of the placenta the space available for implantation was very limited and in close proximity to the internal os of the cervix.

The ultimate course of this patient was satisfactory.

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MULTIPLE DIVERTICULA OF THE PREGNANT UTERUS*

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RELATIVELY few cases of diverticula of the pregnant uterus have been reported. Hess[1] reported one case arising from the posterior wall and one case arising from the right anterolateral wall of pregnant uteri. Hawkins[2] reported a case where the sac arose from the region of the right cornu of a pregnant uterus. Schickele and Freund[3] reported a case where the sac originated from the isthmus of the uterus, lying entirely superior to the attachments of the round ligaments. In all these cases there was painless bleeding from the implanted placenta in the sac of the diverticula.

Jarvis[4] reported a case of diverticulum of the pregnant uterus, originating from the posterior wall, which was diagnosed by laparotomy at approximately three months' gestation. The pregnancy continued to term without untoward symptoms, even though the entire products of conception were contained in the sac. Dorman[5] reported a case of posterior sacculation of the pregnant horn of a bicornuate uterus.

The case being reported here differs from others in two respects: (1) there were two diverticula, and (2) there were no related symptoms during the antepartum period.

Mrs. S., aged 24 years, gravida iii, para ii, whose last menstrual period was Nov. 23, 1950, was first seen on Feb. 5, 1951. The previous pregnancies were noteworthy only for the short labors. Four years previously the patient had delivered an infant weighing 7 pounds, 8 ounces, as a breech after a labor of only ten hours, and 2 years previously an 8 pound infant after a four-hour labor. The past and family histories were otherwise not significant.

The antepartum course was without symptoms. Approximately two months prior to the expected date of delivery, a large soft rounded mass of the same consistency as the uterus was detected in the left pelvic region above the symphysis. It was also noted that the uterus with its contents appeared to lie in a more vertical plane in the right side of the abdomen than usual. X-rays one month prior to term were reported as negative.

The patient entered the hospital at 4:15 P.M. on September 5, stating that pains had commenced about noon, and that she had been losing fluid for three days. Temperature on admission was 100.4° F. There was 1 cm. of dilatation with the presenting part at the pelvic inlet.

The progress of labor was very slow. X-ray of the abdomen was repeated four hours after admission, but no additional information was obtained. The pattern of uterine contraction was abnormal in that the wave of contraction would originate in the fundus and flow down the right side of the uterus, but no contraction could be detected along the left side of the uterus nor in the mass in the left lower abdomen. The quality of contractions was very poor. The patient complained of pain only in the mass, and required more medication than usual to control pain. It was thought that this mass might be an ovarian cyst.

The first stage of labor was completed approximately twenty-four hours from the onset of the first pains. The presenting part had descended to zero or minus 1 station.

After examination, it was felt that delivery through the normal channels was imminent. The situation was re-evaluated after another hour. It was found that the presenting part would descend to a plus 1 station with contractions, but returned to the previous station after the contraction. One minim of Pituitrin was given. An increase in the force of con-

*Presented at the meeting of the Staff of St. Francis Hospital, March 6, 1952.

tractions was noted but also a marked increase in pain localized in the mass was produced. The condition of the mother and fetus remained good throughout the entire labor.

It was decided that labor should be terminated by cesarean section with a diagnosis of dystocia due to ovarian cyst.

At operation, the following pertinent findings were noted:

1. There was a sacculation of the isthmus of the uterus superior to the attachment of the round ligament and of approximately the same size as that portion of the uterus lying inferior to the round ligament. This sac contained the buttocks and lower limbs of the fetus.

2. There was a similar sac originating in the left lateral wall at approximately the level of the internal os, approximately 20 cm. in diameter. A small fibromyoma was seen on the surface of the sac. The anterior shoulder of the fetus, which was lying in right occiputanterior position, was impacted in this sac. The walls of both diverticula were so thin that the fetal small parts were easily visualized through them.

3. The left Fallopian tube, round ligament, ovary, and the upper two-thirds of the broad ligament were absent.

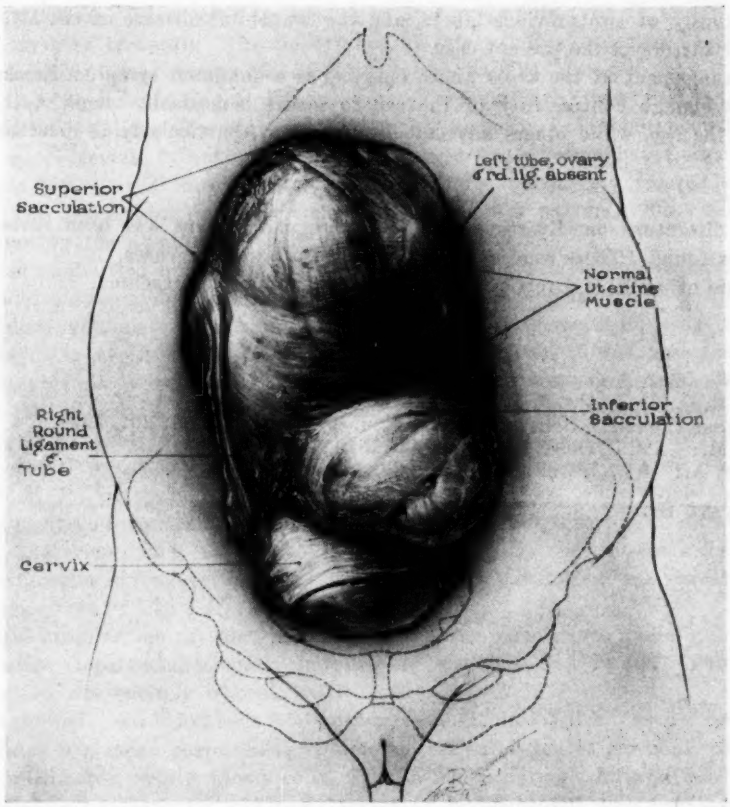

Fig. 1.

The uterus was opened with a vertical incision in the lower segment and a normal viable infant weighing 8 pounds, 4½ ounces, was delivered with some difficulty due to impaction of the shoulder. The placenta was implanted on the posterior wall of the uterus proper. The amniotic fluid was scanty in amount, creamy, and foul smelling.

The postpartum course was uneventful. The temperature declined steadily following delivery and was normal on the third postoperative day. The patient received antibiotics (penicillin and terramycin) prophylactically, intra and post partum. She was discharged on the seventh postoperative day in good condition.

During the next three months, abnormal uterine bleeding developed and a total hysterectomy was performed on Dec. 3, 1951. At this time, no evidence of the superior sacculation was found. On the left lateral wall, in the region of the sacculation, at the level of the internal os, a defect which would admit the tip of the finger was found. This was considered to be the mural defect which permitted formation of the diverticulum. The pathologic diagnosis was: (1) Chronic and subacute myometritis and perimetritis, (2) chronic and subacute perisalpingitis.

The postoperative course was uneventful and the patient was dismissed on the sixth day.

Comment.—Most cases of diverticulum of the pregnant uterus are undiagnosed until laparotomy to determine the cause of bleeding which results from implantation of the placenta within the sac. In the case presented here, there were no symptoms to indicate that the mass, thought to be an ovarian cyst, was connected with the uterus.

The etiology of this condition is obscure. Hess states that it may be due to excessive lysis and invasion of the myometrium by trophoblastic tissues. This may be acceptable when the placenta is implanted in the sac, but in the present case it is difficult to accept this as a factor.

The rapidity of two previous labors, and the congenital absence of the left adnexa may be etiological factors in the present case.

The management of the cases where bleeding is a dominant symptom involves assurance that there is enough contractility of the sac to insure hemostasis. Some authors advocate resection of the sac, while others advocate hysterectomy, particularly if infection is present.

Summary

1. The literature on diverticulum of the pregnant uterus has been reviewed and six previous cases found. There were only single diverticula in these cases.

2. A case of multiple diverticula of the pregnant uterus is presented.

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ACQUIRED HEMOLYTIC ANEMIA IN PREGNANCY TREATED WITH ACTH AND CORTISONE

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THE effectiveness of ACTH and cortisone in the treatment of acquired hemolytic anemia is now well established.[1] We have recently observed a woman with a severe form of acquired hemolytic anemia who was treated with ACTH and cortisone from the second week of her pregnancy until term. Since we were unable to find any similar report, opportunity is taken to describe our case in detail. The importance of this to other types of acquired hemolytic anemia, particularly those due to Rh incompatibility, will be discussed.

A. B., a 32-year-old Negro woman, gravida vii, para v, was first admitted to the Woman's Medical College Hospital in May, 1950, at term and spontaneously delivered a 3 pound, 8 ounce female infant. Her prenatal course was uncomplicated except for a positive serologic test in the third trimester of pregnancy, adequately treated elsewhere with penicillin. The hemoglobin was 8.8 Gm. three days post partum. The patient was discharged following the administration of 500 c.c. whole blood.

She was readmitted in March, 1951, for repair of a cystocele and rectocele. A hematocrit of 32 and a hemoglobin of 9.2 Gm. were found. The repairs were performed and 500 c.c. whole blood administered during the operation. The temperature rose to 101° F. the following day. In typing the patient for another transfusion it was observed that her red cells agglutinated at icebox and room temperature. Cross-matching could be accomplished only if the red cells were washed several times in saline. The second transfusion of whole blood on April 10, 1951, was followed by a shaking chill and a temperature rise to 103° F. A severe hemolytic reaction occurred during the third transfusion on April 14, 1951. Chills, fever of 103.6° F., loin pain, arthralgias, and nausea developed. The urine became deep red and gave a positive benzidine reaction (hemoglobinuria) but returned to normal in 24 hours. Recheck of the cross-match showed no incompatibility, but the patient's red cells demonstrated even greater autoagglutination. A hematologic consultation was requested because of these findings.

Physical examination revealed pallor of the mucous membranes and slight scleral icterus. No adenopathy, hepatosplenomegaly, purpura, or glossitis was found. The remainder of the examination was entirely normal.

Blood showed: red blood cells 2.56 million, hemoglobin 7.5 Gm. (48 per cent), hematocrit 24, color index 0.9, mean corpuscular volume 96, reticulocytes 14 per cent, platelets 190,960 per cubic millimeter, white blood cells, 6,800 with a normal differential. The red cells showed moderate anisocytosis and poikilocytosis. Hypochromia was minimal; polychromatophilia moderate. Spherocytes and polychromatophilic macrocytes were seen. A sternal marrow aspiration revealed a normoblastic hyperplasia consistent with a diagnosis of hemolytic anemia.

Laboratory tests showed: Coombs' test positive; auto- and isoantibodies were found in the patient's serum; serum bilirubin 3.5 mg. per cent; saline fragility normal; acid fragility positive; thrombin fragility negative; sickling test negative; Donath-Landsteiner test negative; Wassermann test negative; x-rays of the chest, gall bladder, gastrointestinal tract, long bones, and intravenous urogram normal.

A diagnosis of acquired hemolytic anemia was made and the patient given 1,575 mg. of ACTH over a period of 22 days (3 days intravenously and 19 days intramuscularly). The

red cell count rose from 1.9 million to 3.0 million; the hemoglobin rose from 6.0 Gm. to 10.0 Gm. The Coombs' test remained positive despite the disappearance of auto- and isoantibodies from the patient's serum.

She was readmitted 4 months later because the red cell count had dropped to 2.29 million with 8.5 Gm. of hemoglobin. The Coombs' test was positive and autoantibodies were found in the serum. ACTH, 20 mg. per day, was administered intravenously. After one month the patient developed moonlike facies, slight transient hypertension, and peripheral edema which disappeared following administration of mercurial diuretics.

On Oct. 3, 1951, 38 days after the reinstitution of ACTH therapy, the patient noticed vaginal bleeding. A gynecological examination revealed an enlarged uterus, compatible with a 2 months' pregnancy. A diagnosis of incomplete abortion was made. She was given Ergotrate, 0.2 mg. three times a day for 3 days, with cessation of bleeding. The amount of ACTH administered now totaled 820 mg.

It was decided to maintain treatment with cortisone, 25 mg. per day. The pregnancy progressed uneventfully with only a hematologic relapse in the fifth month. Cortisone was increased to 200 mg. per day for 2 weeks and slowly diminished to previous maintenance levels. Fluid retention and mild hypertension occurred twice during pregnancy, i.e., in the fifth and sixth months when the patient failed to adhere to a salt-poor diet. An excellent response to salt restriction and the use of mercurial diuretics on one occasion ensued. Corticoid and 17-ketosteroid determinations at various periods throughout pregnancy were always within normal values.

The patient went into labor at the end of the eighth month and spontaneously delivered a 4 pound female infant. There was some difficulty in the establishment of respiration. After 10 minutes of oxygen by positive pressure, Coramine, and aqueous adrenal cortical extract, improvement in the cry and color was noted. The infant was normal except for a slight omphalocele, corrected on the fourth day of life. Desoxycorticosterone acetate was given preoperatively as a precautionary measure, but the infant withstood the operation and general anesthetic without incident.

Comment

The diagnosis of acquired hemolytic anemia was made from the various immunologic and hematologic studies pertinent to this type of anemia. There was a fair response to the first course of ACTH therapy administered intramuscularly. The second course, in which the drug was given intravenously, was attended by an excellent hematologic remission. This persisted, save for one relapse, under maintenance therapy with cortisone. This remission was characterized by a normal red cell count, hemoglobin, and reticulocyte count without the need for further blood transfusions, a negative Coombs' test, and the disappearance of antibodies from the serum.

The development and maintenance of pregnancy during the period of ACTH and cortisone therapy was the unusual feature of our patient's hematologic disorder. The entire pregnancy was essentially normal except for one episode of vaginal bleeding. Water retention occurred twice and was promptly controlled by dietary salt restriction and the use of mercurial diuretics on one occasion. The patient's spontaneous labor was normal in all respects. Bleeding was not excessive. Uterine contractions were not impaired. No undue effect from the general anesthetic was encountered. The child was normal save for a slight omphalocele corrected on the fourth day of life. Signs of adrenal cortical insufficiency were not found.

In conclusion, our patient, treated with ACTH and cortisone from about the second week of pregnancy until term, had a minimum of prenatal complications, and gave birth to a normal, healthy child. This widens the clinical investigative aspect of other hematologic disorders occurring in pregnancy. Hemolytic anemia of the newborn due to Rh incompatibility results from the isoimmunization of the red cells of the fetus by an antibody found in the mother's serum. We therefore attempted to reduce the anti-Rh antibody titer in a pregnant woman who had lost her previous child 4 hours after birth due to hemolytic anemia of the newborn. Although she is still under observation, we can briefly report that her antibody titer, in albumin, has dropped from 1:512 to 1:16. The antibody titer, in saline, has

fallen from 1:64 to 0. This case will be reported in full upon completion of her pregnancy. We believe that cortisone may be of value in the prevention of hemolytic anemia of the newborn.

Summary

1. Acquired hemolytic anemia in pregnancy, treated with ACTH and cortisone, is reported.

2. The effectiveness of cortisone in reducing the anti-Rh antibody titer in a pregnant woman is noted.

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KYPHOSCOLIOTIC HEART DISEASE COMPLICATING PREGNANCY

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THE complication of kyphoscoliotic heart disease is one which is not often seen in conjunction with pregnancy. Mendelson,[1] in 1948, reported an incidence of 0.01 per cent at the New York Lying-In Hospital from 1932 through 1947. Fearl[2] reported a similar incidence of 1 in 12,000 deliveries in a survey covering the years 1940 through 1949. At the Hermann Hospital, from July 1, 1941, through June 30, 1951, there were 40 women admitted with a diagnosis of kyphoscoliosis. Two of these cases were complicated by kyphoscoliotic heart disease, but only one case (included in this paper) was complicated by pregnancy. During this same period there were 18,790 viable deliveries.

Mendelson's report included 7 cases with a total of 13 pregnancies. Eight of the pregnancies were carried to term or near term, with vaginal delivery in 6 instances and cesarean section in 2. In the remaining 5 cases, pregnancy was terminated at from eight to eighteen weeks' gestation because of severe kyphoscoliotic heart disease. Four of these occurred in one patient who had previously carried one pregnancy to term in Class III cardiac status with cardiac failure in the immediate postpartum period; the other in a patient who subsequently carried two pregnancies to term in Class III cardiac status. The latter patient developed cardiac failure with the first pregnancy, did not evidence failure during the second, but developed cardiac failure in the first stage of labor with the third pregnancy. Fearl's report told of 6 patients with a total of 8 pregnancies. There was one fatality in the postpartum period in a patient who had previously had one uneventful pregnancy with delivery at term by cesarean section. A repeat section was done and death was attributed to respiratory failure on the sixteenth postoperative day.

Chapman[3] found that the average age at death was 30 years in 79 patients with kyphoscoliotic heart disease. However, 9 of the 13 pregnancies noted in Mendelson's report occurred at 30 or more years of age.

Vital capacity is frequently used as an index of cardiac reserve and it is variously said to increase or decrease in uncomplicated pregnancy. Beck,[4] for example, states that "the vital capacity is increased from 3260 c.c. in the early months to 3450 c.c. by the end of gestation." In the text of DeLee and Greenhill[5] the statement is made that vital capacity stays within the normal range during pregnancy, but increases an average of 100 c.c. near term. Jensen[6] devotes a space in his book, *The Heart in Pregnancy,* to the effect of pregnancy on vital capacity and lists authors who noted a decrease in vital capacity during pregnancy, others who noted an increase, and still others who found no change. Chapman recorded vital capacity in the range of 560 c.c. to 2,520 c.c. in 12 patients with kyphoscoliotic heart disease, 4 of whom died in pulmonocardiac failure, 6 were living a "very restricted" life, and the remaining 2 had little disability. The lowest recorded readings of vital capacity in the 13 pregnancies complicated by this disease reported by Mendelson ranged from 700 c.c. to 1,500 c.c. In only one patient were the readings less than 1,000 c.c.

Jensen reported data on 50 fatal cases of this complication pregnancy. He presented a table, however, showing cases reported from 1910 to 1936 in which the maternal mortality varied from 3 to 30 per cent. The maternal mortality in Mendelson's 7 patients was zero. Fearl reported one death in 6 cases of kyphoscoliotic heart disease in pregnancy.

Case Report

The patient was a 31-year-old white, unmarried, primigravida who was first seen in the Obstetrical Clinic on Aug. 13, 1951, at 16 weeks' gestation. She gave a history of marked kyphoscoliosis since early childhood and mild shortness of breath with exertion for most of her life. She had never been able to walk over 1 or 2 blocks without becoming dyspneic. There was no family history of congenital deformities.

Physical examination revealed a white woman 56 inches tall who weighed 63 pounds. There were fibromas and nevi generalized over the body and a marked kyphoscoliotic thoracic deformity. The extremities were small and consistent with the slight body build. A cataract in the right eye resulted in total blindness in that eye. The heart sounds were regular and no murmurs were heard. The lungs were clear to auscultation. The abdomen was protuberant and the liver was palpable, but not enlarged. The uterus was enlarged to correspond with the period of amenorrhea. Neurological examination revealed normal findings. Clinical pelvic measurements were within normal limits and x-ray pelvimetry showed an essentially normal pelvis (Figs. 1 and 2).

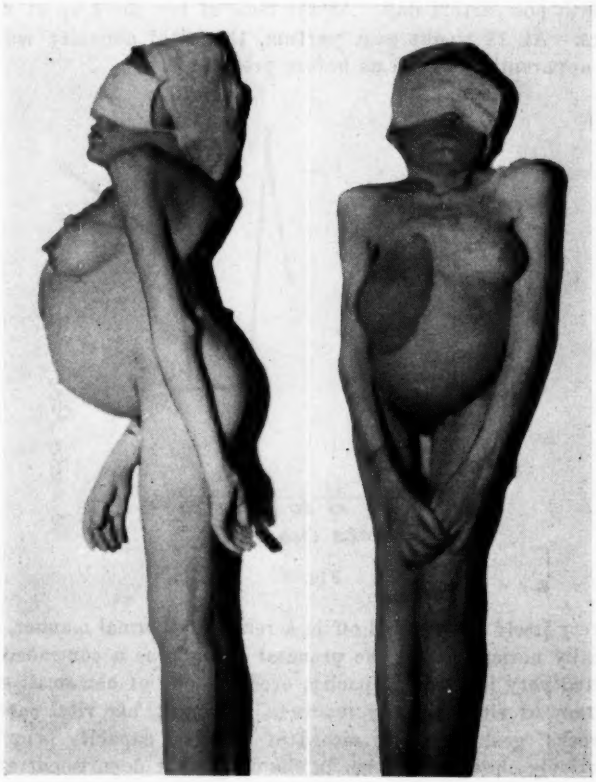

Fig. 1. Fig. 2.

With the onset of pregnancy, the shortness of breath was more marked. By 20 weeks' gestation this was so marked that she was unable to lie flat in bed, and she developed paroxysmal nocturnal dyspnea and a productive cough. Crepitant râles were heard in both lung bases. Diagnoses of kyphoscoliotic heart disease with pulmonocardiac failure versus atelectasis as a result of elevation of the diaphragm without congestive failure were entertained. At

23 weeks' gestation she was hospitalized and treated with diuretics and low-sodium diet. She did not evidence definite cardiac decompensation, the symptoms subsided to some extent, and, after 13 days in the hospital, she was discharged on limited physical activity.

The first recorded vital capacity was at 22 weeks' gestation and was 600 c.c. By 29 weeks, the vital capacity reading dropped to 300 c.c., after rising to 1,000 c.c. at 25 weeks' gestation.

By 35 weeks' gestation, moderate ankle and pedal edema appeared. She had no marked dyspnea and the lung fields were clear. The liver was somewhat enlarged. At 37 weeks, the vital capacity had risen to 670 c.c.

She was hospitalized on four occasions prior to the delivery admission, for a total of 25 hospital days. Each admission was to afford more close observation, because of apprehension on the part of the staff in regard to possible cardiac decompensation, rather than as a result of a marked change in the patient's condition.

She went into labor spontaneously on Jan. 20, 1952, at 39 weeks' gestation and a 6 pound, 15 ounce male child was delivered under pudendal block anesthesia by low forceps, from left occipitoanterior mechanism, over a right mediolateral episiotomy, after a total labor of eleven and one-half hours. Oxygen was given prophylactically at intervals during labor and continuously during delivery. The hospital postpartum course was uncomplicated and she was discharged on the sixth postpartum day. At the time of her check-up at six weeks, she proffered no complaints. At 18 weeks post partum, the vital capacity was 900 c.c. and the cardiac reserve was apparently as good as before pregnancy.

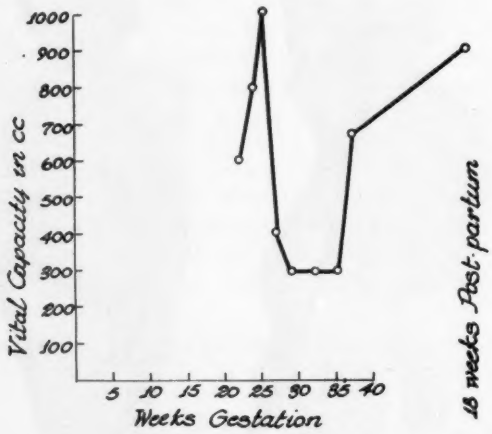

Fig. 3.

While the delivery itself was carried off in a relatively normal manner, as was anticipated in view of the clinically normal pelvis, the prenatal period was a continued source of concern in view of the reported very low vital capacity, even for one of her small stature and despite the notorious inaccuracy of vital capacity readings. At most, her vital capacity was reported as 1,000 c.c. at 25 weeks' gestation. No record of her vital capacity prior to pregnancy was available. With relatively close observation in the outpatient department and several hospital admissions for evaluation, it was never felt that she evidenced definite cardiac failure. The respiratory status, which at times made the patient most uncomfortable, was, even at the times of lowest vital capacity readings, felt not to be of the order to necessitate interruption of the pregnancy.

In conclusion, we feel justified in saying that it is possible to carry a patient with obvious kyphoscoliotic heart disease through pregnancy, labor, delivery, and the puerperium without apparent advance in the disease and that vital capacity is not completely reliable as an index of cardiac or pulmonary reserve.

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MULTIPLE CARTILAGINOUS EXOSTOSES*

A Form of Chondrodysplasia, Complicating Pregnancy

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CHONDRODYSPLASIA, a deforming disorder of bony growth, is represented by three similar but markedly distinct diseases, Ollier's disease, enchondromatosis, and multiple cartilaginous exostoses. Differentiation of the three is best accomplished by studying multiple cartilaginous exostoses and comparing the others to it.

Multiple cartilaginous exostoses is a hereditary deforming disease of bony growth, the chief features of which are: (1) formation of multiple exostoses at the epiphyses of the long bones, the pelvic bones, but never the membranous bones; (2) irregular epiphyseal growth producing shortening and (3) diversion of directional growth.

Multiple cartilaginous exostoses is one of the more common bony dystrophies, some 650 cases having been reported as early as 1915; it is distinctly hereditary, one study comprising 727 cases arising from 163 family trees, an incidence of 64 per cent. The etiology is unknown, but it is believed that a defect in the periosteal sleeve surrounding the epiphyses permits germinal elements to be displaced which continue to grow, producing exostotic nodules. The defect also interferes with epiphyseal function, giving delayed growth in both length and direction. The microscopic pathology of the exostosis is a mass covered first by fibrous tissue layer, then by a layer of cartilage of varying thickness, and, finally, true cancellous bone which is continuous with the bone on which the exostoses are located. The amount of cartilage varies inversely with the degree of calcification which takes place as the patient approaches termination of bony growth, usually between 18 and 25 years.

Symptomatology will be dependent on the deformity produced and on the location and growth of the particular exostosis. Impingement of an exostosis on a vital area can produce any symptom or finding. Treatment will depend upon the location of the offending exostosis and its degree of interference with normal function, resection being performed if indicated. Deformity produced by altered directional growth and shortening, such as varum and valgum deformities of the lower extremities, may be helped by surgical procedures.

By comparison, Ollier's disease and enchondromatosis are quite similar to multiple cartilaginous exostosis, in that they cause bony masses in the long bones and some shortening of the limbs; other findings, however, are distinctly different. Ollier's disease, first described in 1899, is very rare, nonfamilial, and is characterized by unilateral limb shortening and a thickening of the ends of the long bones, which on x-ray are shown to be longitudinal cartilaginous foci with a typical "gouged-out" appearance. These foci ossify with cessation of body growth, thus contributing to a more favorable prognosis. In enchondromatosis, similar cartilaginous foci in the long bones are not longitudinal in character, but are rounded and oval in shape, and do not ossify. These foci continue to grow at a slow rate, demonstrating their neoplastic character and indicating a poor prognosis. Enchondromatosis is nonfamilial.

Of cardinal interest to the obstetrician is the effect which this disease has upon the structure of the bony pelvis. Since the adult bony pelvis is the end result of integrated growth, development, and ossification of the ilium, ischium, and pubes, each possessing its own

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growth centers, it is readily seen how this disease may profoundly affect the formation of the pelvis and produce almost any type of abnormal bony pelvis. The pelvis in this disease is usually irregularly contracted, but, potentially, one of almost any flatness or obliquity may be formed. Static factors serve to distort further the configuration of the pelvis, and exostoses protruding into the pelvis serve to narrow the birth canal even further. The exostoses are usually formed in the region of the growth centers, which are found along the crest of the ilium, at the junction of the ilium and pubis, at the acetabulum, along the crest of the pubis, and in the region of the sacroiliac joint. The prognosis for successful vaginal delivery will be dependent on the absence of cephalopelvic disproportion. In those cases where an irregularly narrowed pelvis is studied with exostoses encroaching upon the birth canal and producing cephalopelvic disproportion, section is the only method of delivery.

A 23-year-old gravida i, para 0, white woman, married for two years, consulted her physician in the first trimester of pregnancy. Her last normal menstrual period was Dec. 22, 1950, and her estimated date of confinement was Sept. 29, 1951. Menstrual history was essentially negative.

The past medical history of the patient revealed no significant features other than the onset of "bony growths" at the age of 8. These were first noticed on both scapulas, growing to about the size of a walnut. In the ensuing years, similar bony swellings, mostly at the ends of the long bones, were noticed on the humeri, femori, tibiae, crests of the ilia, and the clavicles. These apparently grew at a very slow rate, causing no symptomatology and producing only a minimal cosmetic defect. Growth ceased at the age of 18 years. A review of the family history for the past two generations indicated no similar disease, and two brothers of the patient show no evidence of the disease. A review of systemic complaints was essentially negative, except for complaints referable to her pregnancy.

Physical examination showed a temperature 98.8° F., pulse 75, respiration 20, blood pressure 108/82, height 5 feet, six inches, span 64 inches. Examination of the eyes, ears, nose, and throat was negative. The thyroid was normal in size and consistency. The breasts were slightly enlarged and secretion was present.

The lungs were clear to auscultation and percussion. The heart was of normal size, normal sinus rhythm, with no murmurs. The abdomen was soft, showed no masses or tenderness. Liver, kidney, and spleen were not palpable.

External pelvic measurements were as follows: Interspinous 26; intercristal, 27, intertrochanteric 30, external conjugate 20, left oblique 25; right oblique 22; the internal conjugate was 11 cm. Vaginal examination revealed a uterus softened and enlarged to about the size of an eight weeks' pregnancy; during this examination, distinct knobby masses were palpable on all the pelvic bones, but especially the rami of the pubes. Skeletal examination showed a multitude of small knobby bony masses producing a thickening of the ends of most of the long bones. Distinct bony masses were palpable in the following regions: posterior surface of both scapulas, about 3 to 4 cm. in diameter; distal end of the left clavicle, proximal ends of both humeri, region of the third rib, left, in the posterior axillary line, along the crest of both ilia, along the crest of the superior ramus of both pubic bones, at the proximal ends of both femori, at the proximal ends of both tibiae, and at the distal ends of both radial and ulnar bones. Several small masses were palpable in association with some of the metacarpal bones.

X-rays of the pelvis in the first trimester were reported as showing numerous osteochondromas involving all of the bones of the pelvis and the upper portion of both femurs. Other x-rays taken approximately at term showed a term fetus with no changes in the osteochondromas. The anteroposterior diameter was 8½ cm. and the transverse 11 cm. Other x-rays showed large osteochondromas involving both scapulas, humeri, clavicles, and also the first rib on the right and the third rib on the left.

Laboratory reports were as follows: Urinalysis negative, red blood count 3.67; white blood count 9,050, hemoglobin 11.5 Gm., 74 per cent, color index 1.03, normal differential. Calcium 9.1 mg. per cent; inorganic phosphorus 2.9 mg. per cent. Wassermann and Kahn tests were negative.

The diagnosis of multiple cartilaginous exostoses was arrived at and, in view of the contracted pelvis, the patient was considered a candidate for delivery by cesarean section.

Gestation was uneventful until Sept. 25, 1951, at 4:15 A.M. when spontaneous rupture of the membranes occurred. At 5:00 A.M. she began to have pains, which, upon admission to the hospital one hour later, were every three minutes and of strong quality. X-rays taken at this time showed a markedly molded head attempting to dip into the pelvis. Initial rectal examination showed a 50 per cent effaced cervix dilated 2 to 3 cm., with the presenting part in a left occipitotransverse position at minus one station. The fetal heart tones were 140, regular, in the left lower quadrant. Weight of the baby was estimated at 7½ pounds. Examination otherwise was negative.

After 5½ hours of labor, with the membranes ruptured for six hours, during which time the cervix dilated to 3 to 4 cm. and the molded fetal head descended to a minus 1 station, a low cervical cesarean section was performed in the routine manner. A living male infant, weighing 7 pounds, 6 ounces, was delivered, showing a markedly molded head, but otherwise being in good condition. Postoperative course of both mother and child was uneventful, and both were discharged on the sixth postoperative day in good condition.

Summary

1. Chondrodysplasia is discussed, with special reference to its obstetrical significance.

2. A case of multiple cartilaginous exostoses complicating pregnancy and necessitating cesarean section is presented.

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POLIOMYELITIS IN PREGNANCY; DELIVERY OF A PATIENT CONFINED TO A RESPIRATOR

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POLIOMYELITIS is a rare complication of pregnancy but is one which can cause great concern when it does occur. Aycock[1] reports the incidence of pregnancy in all poliomyelitis cases to be less than 1 in 1,000 and the occurrence of poliomyelitis among pregnant women, less than 1 in 50,000. If Brahdy's[2] findings that 4 per cent of all individuals afflicted with poliomyelitis are respirator patients may be applied generally, then hypothetically less than 1 in 1,000,000 pregnant women would have respiratory poliomyelitis. Of these, only a small percentage would be dependent on artificial respiration at the time of delivery.

Case Report.—Mrs. L. J., a 31-year-old, white, para i, whose last menstrual period was June 19, 1950, was admitted to the isolation service of Gallinger Municipal Hospital on July 8, 1950, with the chief complaints of weakness, back pains, headache, and stiff neck of two days' duration. The patient appeared acutely ill with a temperature of 101° F., pulse 100, respirations 28. Physical examination revealed moderate weakening of the intercostal muscles. There was a marked paresis of both sternocleidomastoid muscles and extensors of the shoulders, arms, and forearms. Diaphragmatic excursions were limited. Reflexes were hyperactive throughout.

Laboratory findings: Lumbar puncture, 257 cells with 20 per cent polymorphonuclear leucocytes, 60 per cent lymphocytes, protein 200 mg., culture, negative. Repeated urine and blood studies were normal except for occasional albuminuria and glycosuria. Fasting blood sugar Aug. 23, 1950, was 88 mg.

Within 12 hours after admission, the intercostal involvement became more pronounced and the patient was placed in an artificial respirator. Profound weakness of the muscles of the limbs and abdomen ensued but as the acute phase of the disease subsided, the patient improved sufficiently to allow her removal from the respirator 7 to 10 hours daily.

The patient missed her first period in the respirator, her last menses having occurred approximately three weeks prior to her admission, making her expected date of confinement March 26, 1951.

On Nov. 10, 1950, she was transferred to the Anderson Orthopedic Clinic. She was able to remain out of the respirator for increasing periods of time until the latter part of December when she began to exhibit increasing respiratory embarrassment. The pregnancy was further complicated by cystitis and her increasing difficulty in ingesting sufficient fluids and nourishment.

On Dec. 27, 1950, she was transferred to the Obstetrical Service of Garfield Memorial Hospital where for awhile she tolerated removal from the respirator each day for physiotherapy but these periods became more and more restricted until it was necessary to maintain her in the respirator entirely. She complained of increasing abdominal pressure, gaseous distention, and difficulty in taking food and fluids. An increasing anemia was treated by multiple transfusions. She became disturbed by mild asthmalike attacks and increasing dyspnea. During these periods, increased negative pressure of the respirator, administration of pyribenzamine orally and Adrenalin subcutaneously provided some relief. Repeated courses of Gantrisin were given to control the recurrent pyuria.

On Feb. 8, 1951, at 33 weeks' gestation, the patient went into labor spontaneously. During the first stage which was completed in two hours she remained in the respirator. Near the end of the first stage, she was given ethylene and oxygen with her pains. When dilatation of the cervix was complete, anesthesia was deepened with the use of a face mask and positive pressure and the patient was removed from the respirator and taken to the delivery room. A normal female infant weighing 4 pounds, 10 ounces was delivered by low forceps without difficulty. Respirations improved and positive pressure was discontinued. Following delivery the patient was returned to the respirator.

Her postpartum course was uneventful except for an attack of left pyelonephritis which responded to antibiotics. The infant's condition remained good and she was discharged on the forty-first day weighing 6 pounds, 10 ounces.

The patient's condition gradually improved and she was returned to the Anderson Orthopedic Clinic May 18, 1951. When last seen about four months following her delivery, she was able to remain out of the respirator entirely. She had regained the function of her extremities sufficiently to allow her to feed herself and to bear her weight on her legs. Pelvic examination revealed the uterus to be well involuted and anterior in position.

Comment.—Most writers agree that poliomyelitis has no direct effect on pregnancy or labor. However, complications incident to the disease present obvious dangers. Bladder paralysis with cystitis and ascending infection may lead to pyelonephritis. Kidney stones may develop. Impaired bowel function with distention combined with the enlarging uterus producing pressure on the already poorly functioning diaphragm may produce a serious anoxia. Near term, the removal of the patient from the respirator to allow her to learn to breathe spontaneously is not without danger. McGoogan[3] suggests that, in some cases of poliomyelitis, the strain may retard complete recovery but that, after delivery, the burden having been removed, regeneration may progress more rapidly. In other cases, he believes that the disease might not have been so extensive had the pregnancy not been present.

Since the automatic rhythmic contractions of the uterus are an inherent capacity of the uterus itself, the nerve damage resulting from poliomyelitis does not affect the first stage of labor.

The transmission of the poliomyelitis virus from the mother to the unborn baby appears unlikely since the virus is rarely recoverable from the circulating blood. However, the rare case of poliomyelitis in the newborn of mothers suffering from the acute phase of the disease suggests that the transplacental transmission of the virus is possible.

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CARCINOSARCOMA OF THE ENDOMETRIUM

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CARCINOSARCOMA in any organ is a rare lesion and some individuals question whether or not such a diagnosis is ever warranted. However, most pathologists believe that such a growth may occur and several instances of this lesion in the uterus have been reported. Some of the early reported cases must be excluded as not true carcinosarcomas but rather anaplastic carcinomas or combined carcinoma and sarcoma. There are only about 50 authentic carcinosarcomas of the uterus in the literature.

The histogenesis of this condition is still obscure although much work has been done to determine it. It would seem that Virchow's original concept may be correct, namely, that carcinosarcomas are manifestations of the multipotentiality of the mother tissue and that "sarcoma and carcinoma grow side by side like two branches of the same tree."

Before establishing the diagnosis of carcinosarcoma, one must eliminate the possibility of an anaplastic carcinoma with sarcomatoid characteristics and a collision lesion where carcinoma and sarcoma both arise as separate lesions but coalesce in their development. True carcinosarcomas are single lesions with both components and their metastases may contain either component or both.

Hill and Miller recently emphasized the concept that the presence of large oval or spindle cells having cross striations or multiple acidophilic granules in their cytoplasms definitedly establish a sarcomatous origin since these cells were rhabdomyoblasts. The case herein reported has these features as well as the gross characteristics.

F. P., a 68-year-old white multiparous woman, was admitted to The Brooklyn Hospital June 25, 1950, because of a blood-tinged vaginal discharge for one month. There were no other symptoms except a slight heavy sensation in the lower abdomen.

Her past history was not unusual. She had had no serious illnesses or operations. Her menses began at the age of 14 years, had always been regular every 28 days and lasted three to four days. The menopause occurred at 48 and was not unusual. There had been no vaginal bleeding from the time of the menopause until the onset of the present illness.

The physical examination at admission showed: blood pressure, 175/100; temperature, 98.8° F.; pulse rate, 76; and the respirations, 14. The only abnormal findings were limited to the pelvis. The abdomen was obese and no masses were felt. Vaginal examination revealed normal external genitals, a good pelvic floor, and a one-finger introitus. The cervix was atrophic and healthy. The corpus uteri was anterior, slightly enlarged, symmetrical, and fixed. There were no adnexal masses. The urine examination and blood count were normal. A diagnosis of carcinoma of the endometrium was made.

The day following admission, a uterine curettage was done. The corpus uteri was soft, fixed, and about 10 cm. in greatest diameter. There were no adnexal masses. A small amount of friable endometrium that appeared malignant was obtained. One hundred mg. of radium were placed in the endometrial cavity and removed at the end of 24 hours. A diagnosis of carcinosarcoma was made from the material removed by curettage.

Four days later, an exploratory laporatomy was done. The pelvic peritoneum was covered with small tumor nodules and the left ovary was slightly enlarged and covered with many small papillary masses. The uterus was soft and 10 cm. in diameter, and the right

ovary was buried in dense adhesions. Because the tissues were friable and bleeding was profuse, only a supravaginal hysterectomy and left salpingo-oophorectomy were done. The patient made an uneventful recovery and was discharged on the tenth posthysterectomy day.

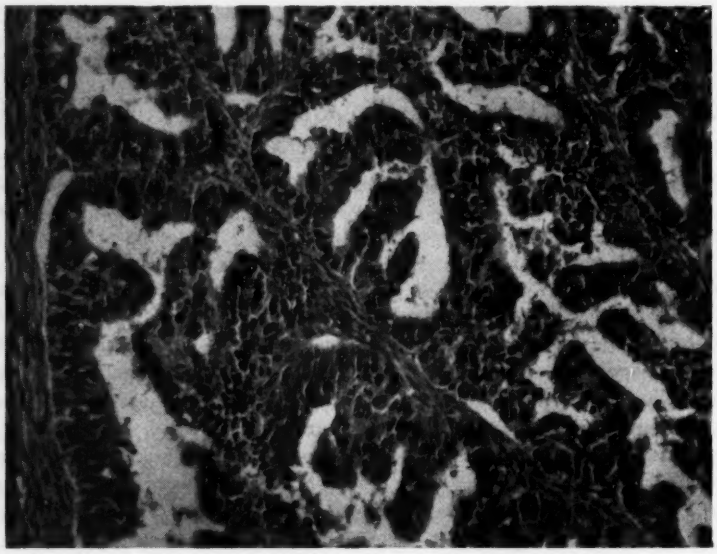

Fig. 1.—Typical papillary adenocarcinoma of endometrium.

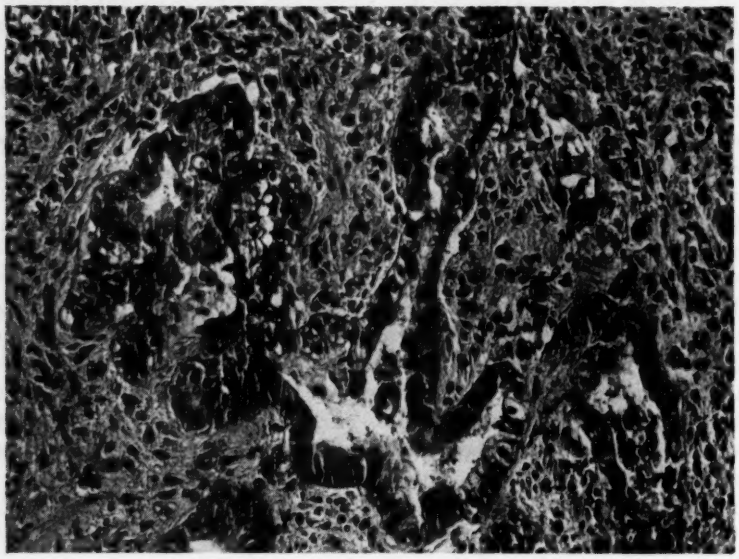

Fig. 2.—Area of the carcinosarcoma showing both components.

Pathological Report.—

Gross Examination: There is a uterus without cervix that has three soft grayish-yellow polypoid tumors attached to the endometrium by slender stalks. The largest, measuring 3 by 2.5 by 2 cm., is attached near the ostium of the left oviduct. The other two tumors average 1.5 cm. in diameter. The endometrium also has raised patchy gray areas varying from 1 to 1.5 cm. The myometrium is soft and contains a small calcified myoma.

There is an ovary measuring 7 by 4 by 3 cm. that has areas of grayish-yellow hemorrhagic material attached to it. There is also an oviduct that is not unusual except for some granular pinkish-gray material attached to the serosa.

Fig. 3.

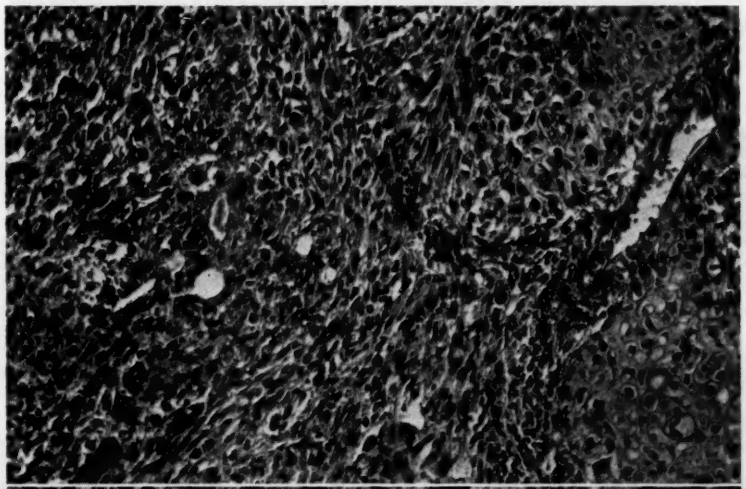

Fig. 4.

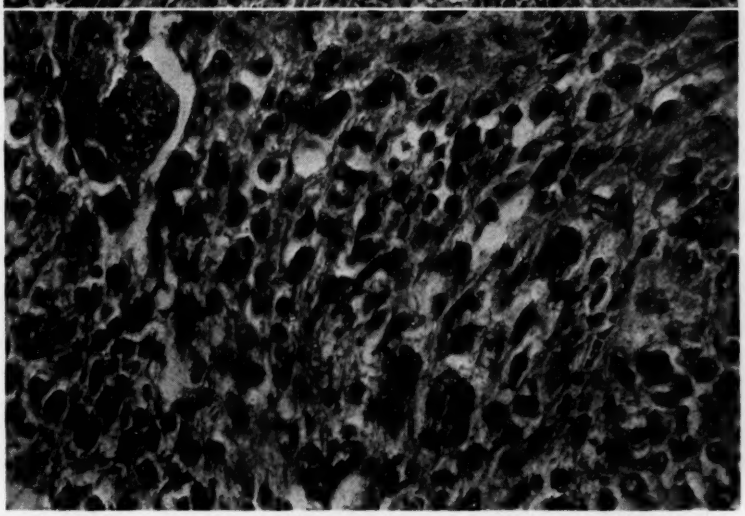

Fig. 3.—Area of cartilage within the carcinosarcoma.
Fig. 4.—High-power view showing the characteristics of the sarcomatous portion.

Microscopic Examination: The endometrium has two distinct lesions separated by normal endometrium. One is a typical papillary adenocarcinoma that is very anaplastic and contains many mitoses. The second lesion is principally sarcomatous and is composed of oval and spindle cells frequently arranged in bundles and containing many mitoses, multinuclear giant tumor cells, and cartilage. However, many areas also have an adenocarcinoma dispersed throughout the sarcoma, and forming an integral part of the tumor. There is no evidence of myometrial involvement.

Masson's trichrome stains demonstrate the presence of large oval or spindle cells having cross striations and interpreted as rhabdomyoblasts. Stains for reticulum reveal the

presence of reticulum in the sarcomatous portion only. The oviduct has exudate and malignant cells on its serosa.

The ovary is atrophic and there is a large area of the serosa involved by a papillary adenocarcinoma of the same type found in the endometrium. There is slight extension into the ovarian stroma.

Diagnoses: Carcinosarcoma of endometrium; papillary adenocarcinoma of endometrium, malignancy Grade III; adenocarcinoma, secondary, of ovary and oviduct; myoma of the uterus.

Fig. 5.

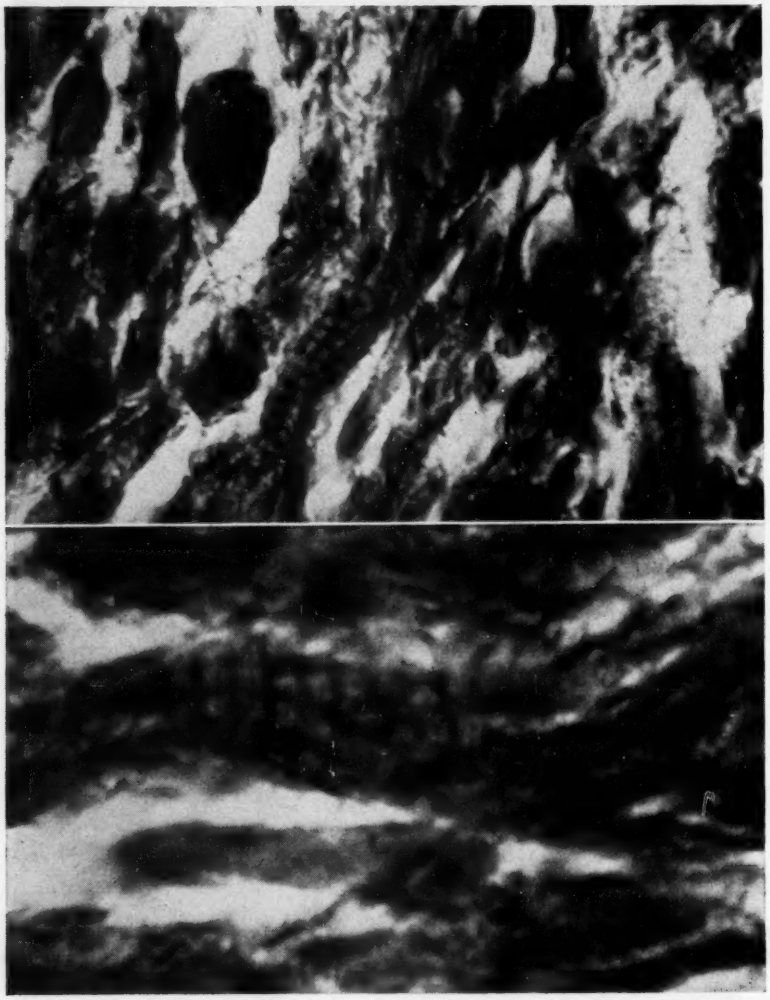

Fig. 6.

Fig. 5.—Large elongated cells having cross striations, interpreted as rhabdomyoblasts.
Fig. 6.—Higher magnification of cells shown in Fig. 5.

Three weeks following the hysterectomy, deep roentgen ray therapy to the pelvis was started and given daily until a total of 12,400 r (in air) had been given.

The patient re-entered the hospital one year later because of nausea, vomiting, abdominal pain and distention of two weeks' duration. The pertinent findings were limited to the abdomen which was distended and had the effects of radiation on the skin of the lower por-

tion. There was a firm, slightly tender mass extending from the symphysis to the umbilicus. Barium enema revealed a large tumor arising from the pelvis and compressing the rectosigmoid and producing a partial intestinal obstruction.

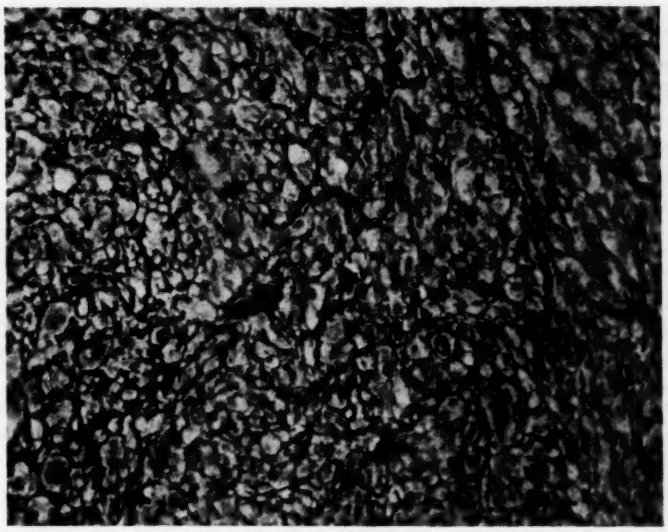

Fig. 7.

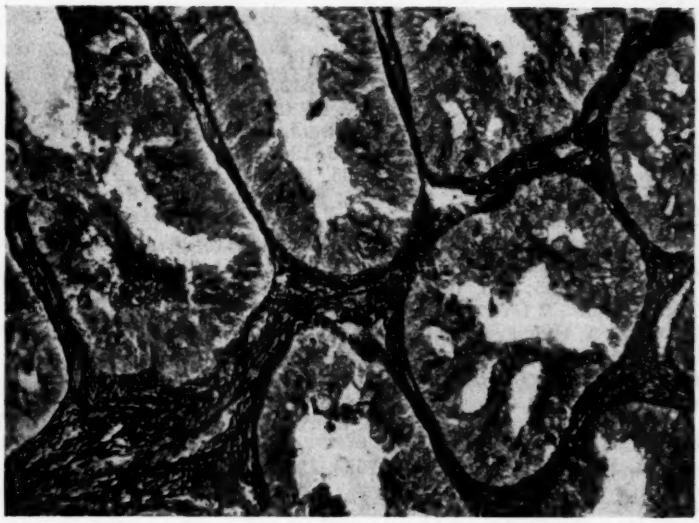

Fig. 8.

Fig. 7.—Perdrau stain of the carcinosarcoma demonstrating diffuse reticulum in the sarcomatous portion.

Fig. 8.—Perdrau stain of the adenocarcinoma revealing reticulum in the supporting connective tissue only.

A diagnosis of carcinomatosis with ascites was made and supportive measures instituted, but the patient rapidly became worse and died one week after her last admission. No postmortem examination was obtained.

Comment.—

This case is of interest not only because of the presence of a carcinosarcoma but also because of a concomitant endometrial adenocarcinoma. These two lesions were located some distance from each other and separated by normal endometrium and thus cannot be considered as collision tumors. Their gross and microscopic appearances were entirely different. The carcinosarcoma was a pedunculated polypoid growth similar to most authentic cases.

It is very likely that cartilage may develop in a carcinoma by a process of metaplasia, but the presence of rhabdomyoblasts would confirm the sarcomatous potentiality of some of the cells. A diligent search should be made for them in all suspected carcinosarcomas.

Recently the terms mixed mesenchymal tumor, and malignant mesenchymoma, have been applied to these tumors. However, since carcinosarcoma is very descriptive of the lesion, and the term is so entrenched in the literature, it is our choice.

In many of the reported cases the patient had received radium therapy for the treatment of benign uterine lesions prior to the discovery of the carcinosarcoma, but this patient had not. As a matter of fact, there were no symptoms of an abnormal uterine condition until one month before admission.

This patient followed the usual course for most patients who have had this lesion. There is no case on record of a patient with carcinosarcoma of the endometrium who has survived five years. Radiation therapy has little if any influence on the process.

It is unfortunate that an autopsy was not obtained so that the character of the metastases could have been known. It is known that the ovary was involved with adenocarcinoma, but possibly at the time of death the sarcomatous component had also spread.

Summary

1. A case of carcinosarcoma of the endometrium has been presented.

2. The finding of rhabdomyoblasts is emphasized as important in establishing the diagnosis.

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429 Clinton Avenue

INTESTINAL EVISCERATION THROUGH THE VAGINAL VAULT SUBSEQUENT TO VAGINAL HYSTERECTOMY*

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Mrs. E. S., aged 51 years, para ii, was operated upon by me June 7, 1948, for almost complete prolapse of the uterus, which had existed since the birth of her second child nine years previously. At a postoperative check-up about 13 months later, July 11, 1949, the note was made: "Vagina good depth and caliber, but on bearing down a high rectocele develops, which annoys her somewhat. The question of reoperation for this was discussed, but the patient decided against it at this time." (In view of the subsequent developments, it seems probable that an element of enterocele may also have been present at this time, although no note was made of it).

On Dec. 15, 1950, following a cold and cough for several days, but without any special straining that she can recall, she noticed something protruding from the vulva and summoned her family physician, Dr. Thomas E. Lindsay, of Richboro, Pa. As he expressed it to me later, he found her lying in bed with "enough intestines to fill a hat" between her legs. With the keen perception of what to do when confronted by an unusual situation, so frequently evinced by the resourceful general practitioner, he hung her head down over the foot of the bed, and was able to replace a good deal, but not all, of the prolapsed bowel. On her arrival at the hospital shortly thereafter, the following note was made by my resident: "Hanging out of the vulva was about two feet of what appears to be small bowel, which was edematous and highly irritable, with passive congestion but no gangrene. The mesenteric vessels were pulsating well; several waves of peristalsis were seen in the prolapsed bowel. The abdomen was not distended." The exposed bowel was covered with warm saline dressings.

When I reached the hospital an hour or so later, these findings were confirmed. Examination in the operating room under spinal anesthesia revealed a circular opening in the vaginal vault barely large enough to admit a finger, through which the loop of bowel was protruding. The edges of this opening were quite sharp and firm, but it was so small that manual replacement of the bowel was not possible; however, by the use of a sponge forceps it was quite easily accomplished. The peritoneum was closed with purse-string sutures in several layers, some redundant vaginal mucosa excised, and the edges approximated with interrupted catgut sutures. A vaginal pack, retention catheter, and Harris tube were inserted, and the patient returned to her room.

Crysticillin and streptomycin were administered for several days. The catheter came out on the second day and was not replaced. The Harris tube was removed on the third day, on which the temperature reached its highest point, 101.6° F. Except for a mild degree of abdominal distention for a day or two, convalescence was smooth and uneventful.

She was discharged on Dec. 27, 1950, the twelfth postoperative day, and has been followed at intervals since. On Sept. 24, 1951, a note was made that she was feeling fine but noticed a slight protrusion again, and examination shows a small rectocele, which condition was unchanged at her last visit, Jan. 14, 1952. There does not appear to be any enterocele at the present time; the vaginal walls seem to be firm and so far, at least, I have not felt that any further surgery is indicated, although if the rectocele increases or an enterocele develops, this may become necessary.

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*Presented at a meeting of the Philadelphia Obstetrical Society, May 1, 1952.

That this is a rather rare condition is evident from the paucity of cases in the literature. In 1951, Kayser, Heaney, and Dahleen reported a case similar in many respects to the one detailed above. They say: "We have been unable to find any references to this condition in the literature. Extensive inquiries have also been unsuccessful." However, in 1948, a case also having many similarities was reported to the Chicago Gynecological Society by Fox, who mentions, without giving specific references, earlier cases of Brose, 1909, and Rieunau, 1933. In an article, also in 1951, on "Lesions of the Vaginal Vault Following Complete Hysterectomy," Beebe and Edwards say that around the turn of the century eight cases were mentioned by Cullen in his discussion of the causes of death following vaginal hysterectomy. They bring out the fact that prolapse of the intestine or oviduct through an opening in the vaginal scar is reported only after vaginal and not after abdominal hysterectomy. It may be surmised, therefore, that, with the increasing popularity of vaginal hysterectomy, which seems to be a definite trend in gynecology today, possibly a somewhat larger number of these cases may be seen in the future.

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1927 SPRUCE STREET

NONGASEOUS ABDOMINAL DISTENTION

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THE serious implications of abdominal distention vary widely. An accurate diagnosis of the cause is urgent for correct therapy and low mortality. The question of surgical intervention is ever present. Abdominal distention of functional origin is always nonoperative and when present with a clinical state of imaginary pregnancy, is readily diagnosed as "phantom or pseudopregnancy." The diagnosis and prompt recognition are elusive when abdominal distention of hysterical origin occurs in a patient who denies pregnancy and presents a history of normal menstrual periods.

The following case is presented as an unusual variant of conversion hysteria with abdominal distention whose counterpart is so easily detected by the obstetrician as pseudocyesis but who is so often subjected to needless and harmful surgery when pregnancy is denied.

B. H., Case 888270, a single 20-year-old white woman, presented herself in the Gynecologic Division of the Henry Ford Hospital, Jan. 24, 1952, with the chief complaint of intermittent abdominal distention and backache.

The initial physical examination was essentially negative throughout. The abdomen was not distended. The liver and spleen were not palpable. No localized tenderness was evident and no abdominal masses were present. McBurney and lower abdominal midline scars were well healed and gave good support. Pelvic examination revealed a virginal introitus. There was a moderate amount of endocervicitis due to the presence of a rubber stem pessary. The uterus was anterior, freely movable, symmetrical, and normal in size. The ovaries were normal in size and position and no adnexal masses were felt. Local paracervical tenderness was secondary to the irritation arising from the intracervical stem pessary.

When it was suggested that we remove the pessary, the patient exclaimed, "if you do, I'll bloat up." She continued, "I bloat up just like I am pregnant and the doctors have found that the pessary prevents it. It lets me drain out." The patient agreed to removal of the pessary and stated she would return immediately if bloating occurred. Six days later, on January 30, she was admitted to the hospital for study and treatment of the severe abdominal distention.

Her first episode of abdominal distention occurred in August, 1946. An appendectomy was performed and the distention subsided during the postoperative period. Shortly thereafter, each menstrual period was characterized by recurrent abdominal distention. Since menarche at the age of 10½ years, the menstrual cycle had been regular with a flow of 4 days occurring every 30 days. Dysmenorrhea was marked, confining the patient to bed for a period of 6 to 7 days during which time the distention always subsided spontaneously. She was admitted to another hospital for a second operation but "nothing was found and they didn't change anything" so far as the swelling was concerned. She changed physicians and a third operation was soon recommended and performed in October, 1947, with "a uterine suspension and excision of ovarian cysts." This afforded temporary relief for several months but by June, 1948, the episodes of abdominal distention were again incapacitating and disturbing as ever. Again, in the hope of alleviating this peculiar abdominal distention, she was subjected, in July, 1948, to uterine suspension

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and excision of ovarian cysts with separation of pelvic adhesions. Apparently the temporary relief from operation was no longer a useful therapeutic procedure for abdominal distention confined her to the hospital for a period of three weeks. She was discharged during a phase of spontaneous improvement but "has never been the same since."

Episodes of premenstrual abdominal distention, emotional outbursts, nausea and vomiting, as well as multiple minor complaints, became more pronounced, confining her to bed for approximately ten days each month. Frequent changes of physicians with the inevitable gamut of Theelin, penicillin, and vitamin B injections, as well as douches, sedatives, vitamins, and other pills, failed to produce any improvement. One physician called it a "pelvic concussion" and said he had seen another case "exactly like her who was relieved by insertion of a cervical stem pessary." This produced an immediate and dramatic response, for as long as the pessary was in place, abdominal distention did not occur. In January, 1952, the patient was placed under psychiatric observation for the first time. Since the psychiatrist referred to her condition as a "phantom pregnancy," she refused to accept this explanation for she knew she "couldn't possibly be pregnant." This explanation was embarrassing to her and the functional implication of her illness brought forth a conflict between her and the psychiatrist. Since the emotional basis of the problem was now in the open, both the patient and her parents desired a final medical opinion and were referred to this hospital.

Physical Examination.—An obese young white woman, aged 20 years, was anxious and weeping but not in distress from pain. She was well oriented to time, person, and place. There was no psychotic behavior and she expressed no delusions or hallucinations. She verbalizes easily and her stream of thought was clear and relevant. She was of average intelligence with evidence of good memory. She had a somewhat defiant attitude, apparently due to the extreme abdominal distention which was obviously embarrassing. She repeatedly brought up the discussion of the emotional possibility in an attempt to convince the examiners that this was "absurd" and that "phantom pregnancy was impossible and ridiculous."

The temperature ranged from normal to 99.2° F.; pulse 80 to 90; respirations 18; weight 173 pounds; height 5 feet, 3½ inches. The pupils were equal and reacted promptly to light and in accommodation. The ears were negative, drums clear. The tonsils were atrophic. The oral pharynx was clear. There was no disease of the cervical glands. The thyroid gland was not enlarged. The trachea was in the midline. The breasts were well developed and no masses were palpable. The lungs were clear throughout to percussion and auscultation. The heart was normal in size, the rhythm was regular, and no murmurs were audible. Blood pressure was 130/84.

The abdomen was distended, measuring 41 inches in circumference at the umbilicus. No masses were palpable. The liver and spleen were not enlarged. Evidence of free fluid was lacking. Peristalsis was present and clearly heard. There was generalized abdominal tenderness without muscle spasm. McBurney and lower abdominal midline scars gave good support without evidence of herniation. Tenderness was present over the lumbar spines which apparently were hyperextended. The reflexes were hyperactive. No pathological reflexes were in evidence.

Pelvic Examination.—The vaginal outlet was virginal. The para-urethral and Bartholin glands were not palpable. A mild endocervicitis resulting from the stem pessary was present. The uterus was small, symmetrical, and freely movable. The adnexa were free of masses and fixation.

Laboratory Studies.—Blood count: hemoglobin 14.6 Gm.; red blood cells 4,880,000; white blood cells, 8,800, with a differential count of 69 per cent polymorphonuclear leukocytes, 2 per cent eosinophils, and 29 per cent small lymphocytes. Urinalysis: specific gravity 1.026, reaction alkaline. Albumin and sugar tests were negative. Microscopically the urine was clear. Kline exclusion test was negative.

The sedimentation rate was 14 mm. in one hour: the hematocrit 45.

Serum albumin was 4.91 mg. and serum globulin 2.45 mg. per 100 c.c.

Course in the Hospital.—During the first day in the hospital the patient wept continuously. Most of this was precipitated by the inconvenience of the nasal tube for gastric suction. Since the suction withdrew only a small amount of clear fluid, very little gas, and had no effect on the distention, it was discontinued after an eighteen-hour period. Although sedatives quieted the patient, no change was evident in the distention. Normal intestinal peristalsis was audible. The patient was not belching and was not swallowing air. A spontaneous bowel movement occurred soon after removal of the gastric suction. There was no vomiting and since the patient desired food, a full diet was prescribed and eaten heartily during the period of hospitalization. Even though the appetite was excellent and normal bowel function was present, still the distention persisted.

Additional studies were performed during this period of continued abdominal distention. Fig. 1 is a photograph of the patient showing the marked distention which continued for a period of eleven days. Circumference of the abdomen at the umbilicus was 41 inches. A flat plate of the abdomen (Fig. 2) revealed: "There are no unusual gas shadows, no unusual soft tissue shadows, and no unusual calcific shadows in the abdomen. Conclusions: the examination of the abdomen is within normal limits." Chest x-ray examination was negative. Fluoroscopy demonstrated free excursion of the diaphragm. Gastrointestinal x-rays showed: "The stomach is of the fishhook type in normal position. It shows regular curvatures. No filling defects are present. The duodenal cap fills well, shows no ulcer nor any evidence of deformity. The duodenal loop is not unusual. The small intestinal series study is negative. The barium enema films show that the colon fills and empties in a normal manner showing no evidence of intrinisic disease" (Fig. 3). Intravenous pyelograms were negative. Residual catheterization was negative thereby ruling out urinary bladder distention. X-ray examination of the dorsal lumbar spine was noteworthy for "there is an exaggeration of the lordosis of the lumbar spine. The center line of the lumbar vertebrae lies considerably anterior to that of the mid-dorsal region.'' The marked lordosis is clearly defined in Fig. 1.

Fig. 1.—This is a photograph of the patient showing the marked abdominal distention which continued for a period of eleven days. Arching of the lumbar spine is present.

On Feb. 2, 1952, a pessary was inserted since the patient was so certain that relief from the distention would follow. Upon return to her room, she immediately removed the pessary when it was found that a doughnut rather than a stem type of pessary had been inserted. The patient was seen by Dr. E. J. Alexander of the Neuropsychiatric Division, who stated that a state of severe conversion hysteria existed. The distention continued. On February 9, after eleven days of abdominal swelling, the original bivalve cervical stem pessary was inserted and that night she stated that gas was escaping from the vagina. The patient was immediately examined. It was impossible to detect any evidence of the passage of gas by vagina or rectum. The next morning the abdomen was normal in size with the circumference of the abdomen measuring 34 inches at the umbilicus (Fig. 4). She was discharged to the

care of her family physician with the recommendation that intensive psychoanalytical therapy held the only possible hope for improvement. It was further recommended that this patient be protected from any surgical procedure performed primarily for this intermittent abdominal distention.

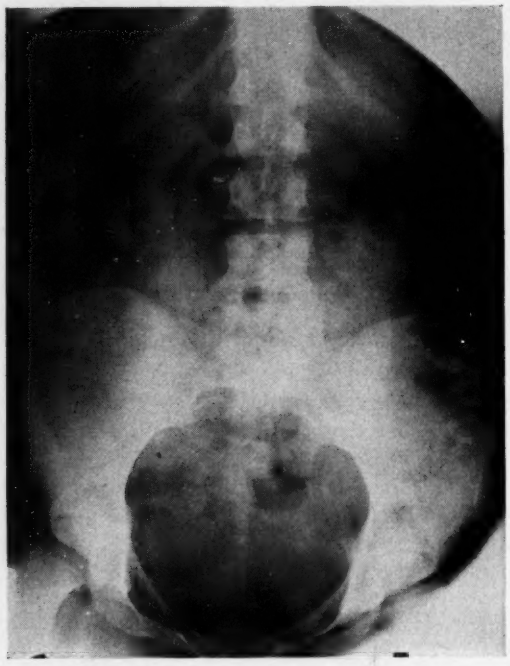

Fig. 2.—Flat plate of the abdomen fails to demonstrate any abnormal gaseous pattern.

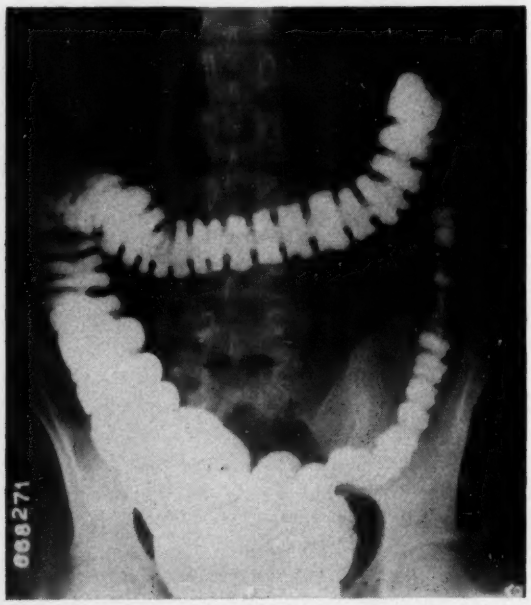

Fig. 3.—The colon fills and empties in a normal manner in the barium enema study.

Comment.—In 1913, Good introduced the term pseudocyesis to describe what is commonly known as false pregnancy even though the condition of nervous bloating had been observed since the time of Hippocrates. Emphasis is placed on the fact that the syndrome of nongaseous distention as presented in our case report is a variant of conversion hysteria differing from pseudocyesis only by the fact that the patient does not believe she is pregnant. Alvarez[1] has presented the most complete review of this unusual clinical state in his report of 92 cases of hysterical nongaseous bloating and points out that this is a variant of pseudocyesis. The earliest clinical case report was made by Bright[2] in 1838 of a hysterical girl with a phantom tumor who was subjected to two abdominal operations for suspected ovarian tumor.

Fig. 4.—The abdomen returned to normal size following the insertion of a cervical stem pessary. Photograph taken at the time of discharge from the hospital.

Clinical studies present sufficient evidence that the etiology arises out of the emotional pattern of the individual even though all manifestations of the syndrome are abdominal. Hypersensitivity, including massive angioneurotic edema, air swallowing, allery, edema, altered intestinal motility, and endocrine theories lack satisfactory explanation. Since there is an absence of excess gas in the digestive tract, the physical changes in the abdomen have been explained by Alvarez[1] as due to a contraction of the muscles lining the back with simultaneous relaxation of the muscles of the anterior abdominal wall. These changes associated with a lordotic posture tend to throw the abdominal contents forward and downward. "Arching forward of the spine," as demonstrated by Alvarez, was present on x-ray examination of our case. Identical findings have been described by Krukenberg, Osler, Gowers, Bargen, and others.[1] Flexion of the knees on the abdomen is likely to overcome the lordosis and cause deflation of the abdomen which has been recognized as a useful diagnostic procedure.

Flat plate of the abdomen, gastrointestinal x-rays, and intubation failed to demonstrate any abnormal gaseous pattern in the intestinal tract. The patient ate a full diet, normal peristalsis was present with the free passage of flatus, and normal bowel movements

occurred during the period of distention. When the intracervical stem pessary was inserted and the patient stated "gas was passing down the womb and out the vagina," even though deflation was occurring, we were unable to demonstrate the passage of gas by vagina or rectum. Similar failures are universally present throughout the literature for the abdominal swelling is not due to excess gas in the intestinal tract.

The uselessness of surgery cannot be overemphasized. Operations performed in the hope of permanent cure have resulted in 100 per cent failure. In the presence of persistent distention, the urge to do something often leads to an "exploratory" operation. All of these patients have been subject to repeated operations and multiple scars on the abdomen should serve as a warning in the absence of demonstrable organic pathology. The gaseous pattern so readily seen in the flat plate of the abdomen in true intestinal obstruction is not present in this syndrome. If the temptation to the surgeon to "look-see" is so strong that operation seems necessary, it is important to remember that, should the abdominal swelling disappear during anesthesia, the proposed operation should be postponed. Examination under anesthesia is a point of differential diagnosis in this condition, as well as pseudocyesis, for as anesthesia proceeds the abdominal enlargement disappears. Witnesses of this phenomenon in the operating room have subsequently played valuable therapeutic and medicolegal roles.

There are many points in common among these patients. The incidence among women approximates 90 per cent, many of whom are nervous, tense, irritable, cry without apparent cause, and in general are constitutionally inadequate. A history of poor sexual adjustment is frequent as well as an inferior emotional family background. The age at onset varies widely and is usually associated with physical or emotional trauma. Attempts to prevent the episodes of bloating are unsuccessful and as the attacks increase in frequency, they may last from a few hours to several weeks. Except for abdominal distention, negative physical examination, x-ray and laboratory findings are the rule. Efforts to relieve the distention are unsuccessful and spontaneous recovery or response to a weird stimulus is not unusual without the passage of gas. The patients are free of symptoms between attacks. Surgery is contraindicated.

Summary and Conclusions

A case of nongaseous abdominal distention is reported.

This syndrome is a variant of conversion hysteria whose counterpart is readily recognized by the obstetrician as pseudocyesis. When pregnancy is denied and the clinical examination is limited solely to the abdominal findings to the exclusion of the emotional pattern of the individual, needless and futile surgery may follow.

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SUCCESSFUL REMOVAL OF A 71 POUND PAPILLARY SEROUS CYSTADENOMA OF THE OVARY

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IN MODERN gynecological practice one rarely encounters a giant ovarian cyst. Pseudomucinous cystadenomas may reach tremendous proportions; Spohn[1] reported one weighing 378 pounds. Strickland[2] encountered a 160 pound pseudomucinous cystadenoma, and Roman[3] and Kidd[4] have reported ovarian cystomas weighing 51¾ pounds and approximately 174 pounds, respectively.

Papillary cystadenomas, according to Erdman and Spaulding,[5] make up 10 to 27.5 per cent of all ovarian cysts. They state that 66.6 per cent of these cysts are either malignant or premalignant.

We wish to report the successful extirpation of a 71 pound papillary serous cystadenoma.

Mrs. F. L. (T47-219514), a 63-year-old Negro woman, was admitted to the hospital on March 7, 1947, complaining of enlargement of the abdomen, inability to walk, and swollen feet. She first noted a small palpable mass in the right lower quadrant in the fall of 1935. The patient visited a physician who, after examination, told her she had a tumor and advised her to have it removed. Because of a strong objection against operation by her husband, surgery was refused. She continued to do hard work and by 1937 the mass had reached the size of a grapefruit. In 1946 the tumor had become so large that she was no longer able to get around and she began to notice dyspnea and swelling of the feet. She was forced to sleep propped up in bed. Finally, at the insistence of members of the family, she consented to come to the hospital for treatment.

The menses had begun at the age of 12 years and had occurred regularly every 28 to 30 days, lasting usually 4 days. The menopause had occurred some 20 years ago. There had not been any vaginal bleeding since. She had had seven pregnancies, all going to term and terminating spontaneously without incident. The review of systems brought forth the following findings: frequent dull headaches, poor appetite with gradual loss of weight over a period of years, increasing dyspnea and swelling of the feet for past two years, polyuria and nocturia for four years. Past history revealed no serious illnesses or operations. She enjoyed excellent health up to the onset of her present illness. Family history was noncontributory.

Physical Findings.—General observations: temperature 98.6° F., pulse rate 80, respirations 19, and blood pressure 175/118. She appeared to be fairly well developed but poorly nourished. The abdomen was tremendously enlarged and the patient was unable to walk or move around without aid. The breasts were generally atrophied and pendulous. The lower margins of the ribs were flared out by pressure from the enlarged abdomen. The lungs were hyperresonant but no râles were elicited. The heart appeared to be slightly enlarged to the left and the aortic second sound was quite loud. The skin over the enlarged abdomen was glistening and tight, and numerous dilated superficial veins were readily seen. The entire abdomen had a cystic feel but there was no noticeable swelling in the flanks as one would expect to see with ascites.

Pelvic Examination.—The labia majora and minora were atrophied and the clitoris was slightly hypertrophied, but within normal limits. A small asymptomatic cystocele was found. The cervix was small and displaced high under the symphysis where it could not be visualized. The uterus and adnexa could not be outlined as such. There was an irregular cystic mass readily palpated posterior to the cervix, filling the entire cul-de-sac and the mass could be palpated extending upward, high on either side of the cervix. A 2 plus pitting edema of the legs was noted.

Laboratory Findings.—On March 7, 1947, urinalysis showed specific gravity 1.016, albumin 0, sugar 0, microscopically an occasional white blood cell per high-power field. The blood hemoglobin was 9 Gm., red blood count 3.15 million, white blood count 4,950 with polymorphonuclear leucocytes 47 per cent, hematocrit 23, sedimentation rate 18 mm. per hour. Kahn and Kolmer tests negative. Blood urea nitrogen was 18.2, serum proteins 7.20. An x-ray of the chest on March 7 was reported as "diaphragm elevated. No definite evidence of pulmonary disease." A flat plate of the abdomen was "not of diagnostic quality." Electrocardiogram on March 10 was "within normal limits."

It was our impression that the patient had a large pseudomucinous ovarian cyst, probably bilateral. She was given a high-calorie, high-vitamin, high-protein diet, and received a 500 c.c. blood transfusion on March 11 and March 12, respectively. Her weight on the day prior to surgery was 175 pounds.

The patient was taken to the operating room on the morning of March 13, 1947. An infusion through an 18 gauge needle was started. Under ethylene and ether anesthesia a long right paramedian incision was made. Intra-abdominal examination revealed a tremendous cystic mass which practically filled the abdomen and pelvis. A small nick was made into the mass and 24,000 c.c. of a brownish-red fluid aspirated. The cyst was dissected away from the peritoneum on all sides. Great difficulty was experienced in freeing the cyst wall from the falciform ligament of the liver and from the sigmoid. Several sutures were required to close a serosal tear in the sigmoid. The uterus was finally brought to view and was found to be enlarged one and one-half times. A supravaginal hysterectomy and right salpingo-oophorectomy were then performed. Following removal of the uterus and right adnexa a cystic structure resembling the left ovary was removed along with the left tube. It was then discovered that the right ureter had been severed. Despite the administration of 1,000 c.c. of blood the patient's blood pressure was down to 70/40. Palpation of the left kidney was done and the left ureter identified and traced intact to the bladder. It was decided that the safest procedure was ligation of the right ureter. This was done and the ligated ends dropped into the abdomen. Oozing surfaces were controlled by hot packs and a rapid reperitonization and closure of the abdomen performed.

The operating time was 1 hour, 38 minutes. The blood pressure was 100/60 at the end of the operation, 1,500 c.c. of whole blood having been administered during the operation.

Dr. W. H. Sternberg, Departments of Pathology of Tulane University and of Charity Hospital, reported that the specimen was an immense cyst which measured 33 cm. in diameter. The fluid contained was brownish and serous. Attached to the side of this cyst was a piece of tissue which was the uterus. The tumor mass arose completely from one ovarian area and the ovarian tissue that remained was not demonstrable, although a small area resembling ovarian stroma was found. The lining of the cyst varied from smooth tan to a rough brownish gray. A second piece of tissue, consisting of a cystic ovary, measuring 13 by 11 by 7 cm., was present. The third piece of tissue, which was not identified, measured 13 by 4 by 0.5 cm. and appeared to be a portion of the cyst wall.

Diagnosis (after microscopic study): bilateral papillary serous cystadenoma; chronic interstitial salpingitis; uterus—myometrium normal, endometrium hypoplastic.

The weight of the right ovarian mass was 3,180 grams and by addition of the total fluid weight removed from the right ovarian tumor it was possible to arrive at an estimated total of 71.082 pounds. The weight of the left ovarian tumor was 3.3 pounds.

The patient's weight on the third postoperative day was 100 pounds or a difference of 75 pounds pre- and postoperatively.

The immediate postoperative period found the patient's condition satisfactory. A transfusion of 500 c.c. of blood was given on arrival to the ward. Nasal oxygen and a Wangensteen suction were started and the urinary output watched carefully. In spite of adequate intravenous fluids the urinary output remained less than 1,000 c.c. per 24 hour period and the blood urea nitrogen rose to 75.0 on the tenth postoperative day. A left parotitis developed on March 17 but was controlled by penicillin and oral hygiene. The maximum daily temperature after the second postoperative day was never over 100° F. Fluids were forced by mouth and vein and the output gradually improved. Cystoscopy performed on March 25 revealed the right ureter to be blocked at 12 to 15 cm. Intravenous pyelograms revealed that neither kidney excreted enough Diodrast to be visualized. Blood urea nitrogen determinations done daily revealed a progressive drop to 29 on March 31, 1947. The patient was considered sufficiently well for discharge on April 1, 1947. She was seen in the postoperative clinic on April 28, 1947. There were no complaints and she had an excellent appetite and was gaining weight. Pelvic examination revealed nothing other than a nonsymptomatic cervical stump. An intravenous pyelogram taken on June 9, 1947, revealed no dye in the right urinary tract. The left kidney presented a moderate concentration of dye. When last seen on Nov. 3, 1947, she weighed 128 pounds. Blood pressure was 170/100 and she was in excellent health. Pelvic examination revealed no obvious recurrences. When last seen on April 27, 1948, she had no complaints and weighed 133½ pounds. Examination revealed a well-healed scar; the abdomen soft with no masses palpable. Pelvic examination revealed the vaginal vault clean with no signs of recurrence. Rectal examination was negative.

Summary

A case of a 71 pound papillary cystadenoma of the ovary is reported. It was removed with some difficulty, but successfully. When last seen fourteen months after surgery, the patient was in excellent health for her age of 63 years.

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3636 St. Charles Avenue

TRAUMATIC FETAL DEATH RESULTING FROM FRACTURED PELVIS

TORBEN SEEAR, M.D., AND CHARLES J. WOEPPEL, M.D., BUFFALO, N. Y.

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TRAUMA to a pregnant woman is very often claimed by the laity as the reason for fetal death. To satisfy our criteria there must be a perforating lesion or a rupture of the uterus, or it must be possible to demonstrate a lesion of the fetus as a result of the trauma.

Woodhull in 1942 reviewed the literature and found forty-six cases of uterine rupture caused by external violence and added a new case; but in all of these cases the fetal death was secondary to the rupture of the uterus.

Ellias in 1950 published the only case in the literature where a fatal lesion of the fetus was found together with a ruptured uterus.

In our case, a fatal lesion of the fetus was obvious but no signs nor symptoms of complete rupture of the uterus were evident at any time.

A survey of the literature reveals no similar case; we therefore feel that this case should be reported not only for its rarity but also because of the spontaneous vaginal delivery despite a grossly fractured pelvis.

Mrs. M. D. (File No. 21197-A), a 21-year-old para ii, gravida iii, was admitted to the Obstetrical Service of the Edward J. Meyer Memorial Hospital on Dec. 15, 1951. Her last menstrual period occurred on April 16, 1951, and the estimated date of confinement was Jan. 24, 1952. Previous pregnancies and deliveries had been normal, the largest infant, weighing 8 pounds, 12 ounces, delivered in 1950. The present pregnancy had been uneventful to the time of the accident.

This patient, while riding in the front seat of an automobile which was involved in a head-on collision, was thrown against the front panel and windshield. She was admitted at 8:30 P.M. complaining of pain in the lumbosacral area and showed lacerations of the forehead and the right wrist. There was no evidence of labor and the uterus was of normal consistency and not tender. There was no vaginal bleeding and the fetal heart sounds were heard in the left lower quadrant. The patient was not in shock; immediate attention was given the lacerations.

X-ray examination of the pelvis was then performed, and the findings showed: (File No. 51-30470) Examination of the sacro-iliac joints showed marked irregularity of the right sacro-iliac joint indicating the presence of fracture of the upper portion of the sacrum and ilium on that side. There was also noted a fracture of the left pubis and ischium, the symphysis was separated approximately 2 cm., and there was marked displacement of the fragment downward. There was noted a fetus close to term in a cephalic presentation.

At 9:00 P.M. of the same day this patient began having labor pains at about 3 minute intervals. A rectal examination revealed the vertex presenting just above the spines, the cervix was thick and 1 cm. dilated. The fetal heart sounds were in the left lower quadrant. She was given morphine sulfate, 0.015 Gm. hypodermically, in an effort to stop the labor. At 10:00 P.M. she had contractions every 3 minutes, of good quality, and some bloody show was evident; the uterus continued to be nontender and relaxed between contractions. The cervix was now effaced and 2 cm. dilated. No fetal heart sounds were

heard at this time. At midnight contractions were of good quality and again no fetal heart sounds were audible. There was some vaginal bleeding; however, the blood pressure was 120/80 and the pulse 80. At 1:30 A.M. the head was on the perineum and at 1:48 A.M. the patient was delivered spontaneously of a stillborn male infant, 7 pounds, 1½ ounces, from a left occipitoanterior position. Immediately after delivery 300 c.c. of blood clots were passed, and this was followed by continuous oozing. Digital examination of the generative tract showed no lacerations; the uterus was then packed with plain gauze. The placenta showed clot covering 15 per cent of the maternal surface. The blood pressure post partum was 100/70 and 1,000 c.c. of compatible blood was given. The packing was removed twelve hours post partum. There was slight oozing for 24 hours, however, the blood pressure and pulse were normal. The abdomen was slightly distended after 12 hours but was relieved by insertion of a rectal tube. Penicillin S-R, 400,000 units daily, and streptomycin, 0.5 Gm. twice a day, were administered for nine days. Small amounts of old blood clots were passed by the patient for two weeks post partum but no signs of peritoneal irritation appeared.

The fractures were treated with a pelvic sling and recovery was uneventful.

Pelvic examination on Feb. 7, 1952, showed the uterus well involuted and adnexa negative. The fractures were not palpable. The patient had her first menstrual period on Feb. 14, 1952. This period was normal in all aspects except that it was accompanied by more severe cramps than usually experienced in previous periods. In subsequent periods the patient has been complaining of severe dysmenorrhea but examination on July 18, 1952, revealed the uterus to be of normal size in normal position. The adnexa were negative; the fracture sites could not be palpated.

Examination of the fetus immediately post partum revealed the skull to be moderately molded. There was an extremely mobile fracture of the right side of the skull. Findings at autopsy were a fracture in the right parietal region which extended from the anterior to the posterior fontanel forming a "V" with the apex 2 cm. above the temporal bone. It measured 11 cm. The dura and the periosteum were torn and the blood and brain exuded into the subgaleal space. The left parietal region showed a hematoma into the dura.

Comment.—This case presented a problem in management of labor and mode of delivery. There were no symptoms or signs of rupture of the uterus or severe injury to the bladder or other viscera. The patient had previously delivered large babies following short labors and the loose fragment did not seem to obstruct the pelvis. These considerations made us abandon cesarean section in the interest of the mother and the loss of fetal heart sounds early in labor was felt to be an absolute deterrent to section, in favor of the infant.

Basing our judgment on these considerations, delivery by way of the birth canal was decided upon.

The immediate correlation between the sustained trauma and the death of the fetus in this case is so obvious that there is no room for doubt. It is felt that the mechanism of the fetal skull fracture was the result of direct depression of the loose fragment of the maternal pelvis against the uterus and secondarily against the fetal skull while the head was presenting in a left occipitotransverse position in the pelvic inlet. Examination of the birth canal and the fact that the patient never developed any signs of intraperitoneal bleeding showed that this was accomplished without laceration of the uterus.

Appreciation is extended to the Radiology Department, Dr. E. G. Eschner, and the Pathology Department, Dr. S. Sanes, at the Edward J. Meyer Memorial Hospital for their cooperation.

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SIMULTANEOUS INTRAUTERINE AND EXTRAUTERINE PREGNANCY

C. ALLEN ALEXANDER, M.D., KALAMAZOO, MICH.

(From the Borgess Hospital)

AT BORGESS Hospital, with 250 beds, from 1915 to 1951, a span of 36 years, there were 26,559 live births. There is only one recorded instance of a simultaneous intrauterine and extrauterine pregnancy. From 1945 to 1952, a span of 7 years, there were 10,425 live births and 69 cases of extrauterine pregnancy.

This 24-year-old mother of two children, ages 5 and 3 years, was seen at Borgess Hospital on March 30, 1952, at about 12:00 noon. She stated that she was having some dark red thick vaginal discharge and pain in the right side, low in the abdomen. Her last menstrual period, which was the regular one, was on Feb. 2. It was unusual in that it had its onset with a gush of blood and was quite profuse in amount. She bled so much this time that she was compelled to go to bed. Her usual periods were irregular in their interval, often about 21 to 24 days, even to an interval of 30 days, with a duration of 4 to 5 days, with moderate flow and some cramps accompanied by lower abdominal discomfort and backache. However, the February flow was accompanied by considerably more severe objective symptoms and the amount was unusually large. She had expected her March period approximately March 2. This did not occur and she had the subjective symptoms of pregnancy which she had experienced before. Approximately one week before, on March 23, she began to have right-sided abdominal pain which was cramplike in nature and at the same time she began to bleed profusely. She went to bed. This continued for about 3 days and gradually subsided to a brownish-red discharge. This was the same type she was having now. However, the righ-sided lower abdominal cramps were continuous. There were times when they were more severe than others. She had felt quite weak but she had not fainted at any time. She denied any symptoms referable to the cardiorespiratory, genitourinary, or neuromuscular system, except for being a little nervous.

Past History.—She had had scarlet fever, followed by endocarditis at age 10. Appendectomy at age 14. Hemorrhoidectomy at age 22. Two normal pregnancies which resulted in female children, ages 3 and 5. There had been no abortions and no miscarriages.

Family History.—Her parents were living and well. Two sisters were living and well. There were no twin pregnancies anywhere in the family history.

Physical Examination.—This revealed a very intelligent young woman who did not appear acutely ill. Positive signs were: soft systolic basal murmur which was heard over the mitral and was transmitted to the axilla. None of the secondary signs of pregnancy were present on the breasts. The abdomen was flat, with an appendectomy scar, well healed and nontender. The liver, kidneys, and spleen were not palpable. The cervix was soft, bluish, and exuding from it was a brownish-red thick discharge. The uterus appeared to be enlarged to about half again its normal size, with third-degree retroversion, tender but not palpable. The left ovary could be palpated but was not tender. On the right there was a small, exquisitely tender mass, which was thought to be either a cystic ovary or a tubal mass. Rectovaginal examination did not add to this information.

The patient was admitted to the hospital with a suspicion of probable ectopic pregnancy.

Laboratory Findings.—The hemoglobin was 11.6 Gm., 73 per cent; red blood cells 3,580,000. Color index 0.9; white blood cells 7,500; lymphocytes 41, neutrophils 59, eosinophils and basophils: none. The Schilling index was 0-0-0-69. The Kahn test was negative. The sedimentation rate was 18 mm. in 1 hour, Wintrobe method, uncorrected. The volume of packed cells was 41 c.c. per 100 c.c., the corrected sedimentation rate 16 mm.

March 31, 1952.—The patient appeared comfortable and did not complain of right-sided pain. However, she continued to bleed vaginally. It was decided that dilatation and curettement of the uterus were indicated. This was done and approximately one ounce of a decidua-like material was obtained. On palpation under anesthetic, the right sided mass could again be felt, as could the left ovary. The uterine cavity was packed with iodoform gauze and the patient put back to bed in good condition.

April 1, 1952.—The patient was slightly nauseated but complained only mildly of right-sided discomfort. The pack was removed. There was no bleeding.

April 2, 1952.—At 3:00 A.M., the patient was sleeping soundly, according to the nurse, when she awakened very suddenly screaming with severe pain in the right lower abdomen. She stated that she got up to go to the bathroom a little earlier and passed a great many blood clots, then went back to bed and was awakened with severe pain. On examination at this time the radial pulse was absent, blood pressure was 70/35, and color very pale.

I saw her about 20 minutes later and confirmed the fact that she was in surgical shock, doubtless due to massive intra-abdominal hemorrhage. Supportive therapy was immediately instituted, consisting of plasma until whole blood was obtained. After getting 2½ pints of blood into the patient and three units of plasma, she was taken to the operating room and the abdomen was opened.

Operative Findings.—The abdominal cavity was filled with blood. There were a few clots in the pelvis but mostly liquid blood. The uterus was found to be enlarged to about half again its normal size. There was a rupture in the mid-portion of the right tube and a small fetus, about one inch in length, lay within its membrane. There was oozing of dark blood from the fimbriated end of the tube. Corpus luteum was in the right ovary. A right salpingectomy was done, most of the blood was removed from the pelvis, and the abdomen was closed.

Pathological Report.—Two laboratory reports, two days apart, clearly showed: (1) Placenta, in a quantity that could be recognized grossly, as well as microscopically, was first passed from the uterus, and (2) an intact amniotic sac was removed from the abdomen following a tubal abortion. The reality of simultaneous uterine and tubal pregnancies is therefore beyond question.

The postoperative convalescence of this patient was fairly uneventful. She was discharged in good condition on April 12, 1952, after a hospital stay of 13 days.

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Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Review of New Books

EDITED BY PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

Miscellaneous

Blutgruppenbestimmung und Bluttransfusion. By Peter Dahr, Professor an der Universität Gottingen, and E. Regenbogen, Chefarzt der Med. Klinik, Abt. A, Stadt. Krankenanstalten Osnabruck. Ed. 2, 256 pages with 16 illustrations. Stuttgart, 1952, Georg Thieme Verlag. DM 16.50.

This small book is composed of two monographs. Dahr's monograph deals with the complications of blood transfusion and their prevention. The ABO, Rh, and more recently discovered blood systems are discussed briefly but adequately. Considerable space is allotted to descriptions of techniques of blood grouping and cross-matching. Infections transmissible by blood transfusion are also treated at some length. The final section of the monograph deals with exchange transfusion, for which Dahr attempts to outline indications.

Regenbogen's monograph deals with techniques, indications, and contraindications for blood transfusion. With the exception of the part dealing with exchange transfusion, the discussion of techniques seems merely of academic interest to workers who have access to equipment in this country. The remainder of the monograph is of general interest.

Specialists in the field of blood groups and blood transfusions may find this a worthwhile volume for reference. Others will prefer to consult the excellent books on the subject which have been published recently in England and in this country.

EVA ABLESON

Sex After Forty. By S. A. Lewin, M.D., and John Gilmore, Ph.D. Introduction by the Reverend Dr. Russel L. Dicks, Professor of Pastoral Care, Duke University. Pp. 200, with 40 illustrations. New York, 1952, Medical Research Press. $3.50.

This is a book for all people, meant to be informative and reassuring. It explains the menopause and the male climacteric. In the authors' view this last is a common personal experience and a clinical entity. The discussion of sex is good and should often relieve anxiety. The text is simple, the chapters short, the illustrations excellent for the purpose.

While *Sex After Forty* is the title, much of the book is about life after forty. Or perhaps it is just that good hygiene, good grooming, escaping obesity, helpful hobbies, adult education, zest for life, all make for better sex experience.

Twenty case histories fill thirty pages. Some of the book's best teaching is here. For "your emotional problems," counseling is advised, and explained. Counseling services in many states are listed. A good glossary and index complete the book. It can be highly recommended by doctors or other counselors.

LOVETT DEWEES

Physiopathology of the Blood—Protein—Plasma in Pregnancy (Fisiopathologia Gravidica dell' Emoprotidoplasma). By Prof. Guido Micale, assistant and associate in Obstetric and Gynecologic Clinic of Messina, Italy. Pp. 208, no illustrations. Bologna, 1952, Licinio Cappelli. 1,500 lira.

This volume has presented the subject matter of blood proteins in pregnancy in an academic and scientific manner. The bibliography is extensive. Much work and study have been devoted to this subject. There are eight chapters dealing with the normal changes in blood proteins in pregnancy and also those associated with complications. According to the author, a disturbance in the normal relations of blood proteins is the first evidence from which all symptoms are derived. This condition is seen especially in the third trimester of pregnancy with the presence of edema and nephropathology.

The normal blood is described as composed of a large number of pure proteins that differ from one another not only in chemical composition but also in solubility, molecular weight, etc. It is important in a study of blood proteins to include the lipoids and lipoid proteins.

Alterations in blood proteins can result from the periphral circulation or from functional alterations of blood proteinplasma centers. The latter are the liver, reticulo-endothelial system, and the bone marrow. These alterations can be detected by macroscopic, chemical, physical, polarographic, ultracentrifugal, precipitation tests, etc. The end results of disproteinemia are manifested by alterations in blood pressure, metabolism, blood-carrying elements, blood coagulation, and nephritides.

Clinically, in the third trimester of normal pregnancy, there is an increase in blood proteins with a decrease of blood albumin, an increase in globulins and fibrinogen. In hypertension with edema from kidney damage there is an increase of abnormal proteins. The abnormal proteins result from the disturbed protein metabolism in the ovum, maternal tissue, and the liver. There is a deficient production of plasma in the bone marrow during pregnancy with an increased permeability of the capillaries to these proteins. These changes are all increased in the presence of edema and renal disturbance. In hypertension and eclampsia the hepatic influence plays an important role in protein metabolism.

Changes in blood plasma in pregnancy cause albuminuria which is the result of abnormal plasma proteins permeating through the renal filter. With the decrease in proteins, the blood pressure is lowered followed by water retention and finally edema. There is an interchange of proteins from the plasma to the tissues and vice versa in both maternal and fetal organisms. The increase of proteins and fats in the blood plasma is physiological. The plasma also shows a decrease in calcium and an increase in copper and iron. The increase in coagulation of the blood is due to the increase in fibrinogen.

After discussing various changes in blood proteins resulting in clinical syndromes, the last chapter outlines therapy in four classifications: (1) prophylaxis, (2) casual therapy, (3) substitute therapy, and (4) symptomatic therapy.

This book should be of great interest to students of blood chemistry and obstetricians.

VINCENT P. MAZZOLA

The Origin of Life and the Evolution of Living Things. An Environmental Theory. By Olan R. Hyndman, M.D. Pp. 648, with 41 illustrations. New York, 1952, Philosophical Library. $8.75.

When an experienced neurosurgeon takes the time out of a busy life to compose a long study of biological evolution, the product must be considered seriously. An analysis of physical and chemical interactions in life processes is interwoven into a philosophical, often metaphysical concept of the origin of life and the development of living organisms. The author obviously does not consider the current theories of genetic mutation as the sole or most likely cause of the formation of new species. His skillful rendition of the interaction of the internal environment of the organism with the fluid and changing external environment indicates clearly his support of the basic tenets of Lamarck's biological philosophy.

This volume is not one to entertain the reader for a leisurely hour, and is not likely to prove popular for fireside enjoyment. The text and the arguments are well organized and documented, but the book must be studied carefully, because each section is dependent on the preceding one. To students of the physiology of reproduction, a section of nearly 150 pages devoted to the significance of the development of bisexual modes of reproduction, illustrated with original diagrams by the author, will be of interest.

To the student of life processes who possesses a philosophical and speculative bent, a careful study of this book may be rewarding. The practical reader will probably not long be diverted.

EARL T. ENGLE

Fuer und wider die Sterilisierung aus eugenischer Indikation. By Dr. Hans Nachtsheim, Professor der Allgemeinen Biologie und Genetik, Berlin. Pp. 64 with 4 illustrations. Stuttgart, 1952, Georg Thieme, Verlag. German Marks 5.70.

The author of the monograph, *The Eugenic Indication for Sterilization,* starts with the critical discussion of the standing laws and the present practice of eugenic sterilization in different countries. In his opinion, sterilization of carriers of certain serious hereditary diseases should be ordered and steadily controlled by law. He compares the States of America which have classical sterilization laws with European countries. The favorable influence of sterilization on the elimination of hereditary diseases is academically discussed; even if sterilization does not remove abruptly the diseases in question, a considerable improvement in the future can be expected. In spite of the amazing progress of medicine, it is not possible to eradicate completely any disease in the world by prophylaxis. But this does not mean that the respective hygienic measures should be abandoned. The main object of eugenic sterilization is the drastic reduction of progress and spreading of serious hereditary diseases. Certain groups do not agree with sterilization; their reasons are critically discussed and bluntly rejected by the author in a highly scientific manner. The suggestion to keep carriers of hereditary diseases in institutions is considered as cruel and inhuman; eugenic sterilization is more ethical than imprisonment for a lifetime, as long as the patients do not endanger others. There is no doubt that this booklet, written by an exceptionally qualified scientist, gives the physician who understands the German language the chance to study the problem of sterilization from different angles and to compare critically the interesting arguments which are in favor and which are against the legal regulation of eugenic sterilization.

ROBERT TAUBER

Psychosexual Functions in Women. By Therese Benedek, M.D., The Institute for Psychoanalysis, Chicago. Pp. 435. New York, 1952, The Ronald Press Co. $10.00.

In 1939, the author of this book, in collaboration with Dr. Boris B. Rubenstein, studied the psychosexual manifestations of the ovarian functions. Through daily temperature charts and vaginal smears the state of the ovarian cycle was established in a number of women who were undergoing some psychonalysis at the time. The material of the psychoanalyses was analyzed in an attempt to ascertain whether there are changes and fluctuations in the psychosexual manifestations of the patients, particularly in relation to the ovarian cycle. From both of these studies made independently, and then compared, it was found that they almost exactly coincided. Both the psychological method and the laboratory method were able to establish the significant stages of the ovarian function. It was found that sexual behavior in women is motivated by a great variety of factors. The biological tendencies are disguised and modified by cultural patterns as well as by various developmental phenomena which determine the individual variations of sexuality. The studies established that (1 the emotional manifestations of the sexual drive, like the reproductive function itself, are stimulated by gonad hormones; (2) parallel with the production of estrogen, an active extroverted heterosexual tendency motivates the behavior; (3) parallel with the progestin phase, the psychosexual energy is directed inwardly as a

passive, receptive, and retentive tendency; (4) parallel with the hormonal cycle an emotional cycle evolves. The hormonal and emotional cycles together represent the sexual cycle.

This book represents continued work on observation following up the studies begun in 1939. In fact, the first part of the book repeats the work of that time. It combines a histological and a psychological method for the purpose of investigating correlations between endocrine and psychic functions. There is fully reported case material with comments and conclusions. There is a chapter on the psychosomatic implications of the primary unit: mother-child. There is also a chapter on the climacterium. Additionally, there are chapters on "The Functions of the Sexual Apparatus and Their Disturbances" and a concluding chapter on "Psychophysiological Problems of Motherhood." There are a good bibliography and index.

The author's study of the sexual cycle brings her to the following conclusions: (1) Hormones stimulate specific emotional responses. (2) Psychological factors which determine the personality development exert influence upon the hormonal regulation. (3) The interaction between psychological and hormonal regulation is continuous. This means that the sexual cycle once established does not remain an unchanging characteristic of the individual; emotions motivated by sexual drive as well as by other aspirations of the personality (ego drive) may exert conflicting influences upon the hormonal processes; they may change, accelerate, or retard the evolution of the cycle and may cause various shifts and irregularities.

The material covered in this book should be of great interest to the gynecologist, the endocrinologist, the internist, the general practitioner—in fact, to anyone interested in the psychosexual functions in women.

O. SPURGEON ENGLISH

Selected Abstracts

EDITED BY GEORGE W. KOSMAK, M.D., NEW YORK, N. Y.

Labor, Management, Complications

Carreno, E.: Clinical and Experimental Confirmation of the Oxytocic Action of Sparteine Sulfate, Bol. Soc. chilena de obst. y ginec. **15**: 216, 1950.

The author used sparteine sulfate in 201 cases of uterine inertia. The membranes were intact in 15 cases and ruptured in 186. The drug was exhibited during the first stage of labor in 46 cases, and during the second stage in 118. The remaining patients had no cervical dilatation when the drug was used.

Results were best when the patients already had cervical dilatation or were in the second stage of labor. The effect was more pronounced when the drug was used intravenously, but the intramuscular route was employed in most cases. There is some danger of tetanic uterine contraction following intravenous injection.

The effective single dose was found to be 150 to 200 mg. (1 c.c. of a 20 per cent solution).

Sparteine sulfate was found to be ineffective for the induction of labor.

Intraovular transparietoabdominal hysteromyography was carried out in 46 cases, and the author presents some illustrative kymographic tracings showing the increase in frequency and intensity of uterine contractions following the use of sparteine sulfate.

The author concludes that sparteine sulfate is a useful agent for the reactivation and intensification of labor contractions. Its action is usually mild, regular, and persistent. There is a latent period of 5 to 10 minutes between injection of the drug and demonstrable effect. Intravenous use produced frank hypertonicity, and this route is advised only at the end of the second stage or during the third stage of labor.

The author proposes to investigate the intravenous drip method with this drug.

MAGIN SAGARRA

Aguilo, J.: The Antispasmodic Action of Novocain in Labor, Bol. Soc. chilena de obst. y ginec. **15**: 253, 1950.

Intravenous Novocaine was given to 100 patients in the first stage of labor, 20 c.c. of a 2 per cent solution being used. The injection was given slowly, in 10 minutes. This dose was used one to three times at hourly intervals; most patients received one or two doses.

The use of Novocain was avoided in pre-eclamptic and hypertensive patients because of the observation that intravenous Novocain has a hypertensive effect in some cases.

A favorable effect in promoting cervical dilatation was observed in 81 per cent of the cases. No analgesic effect was observed with the doses employed.

There was no appreciable change in the character, frequency, or intensity of uterine contractions. No change in the character of the second and third stages of labor was noted. The drug had no apparent deleterious effect upon the fetus.

Side effects were minimal and transient. These consisted of nausea, dizziness, visual disturbances, buzzing in the ears, paresthetic sensations, slight cyanosis of the fingers, and psychic excitement. Occasionally a tachycardia of 100 to 120 was observed. A rise of 10 to 20 mm. in blood pressure was present in some cases. Some of these reactions can be decreased or avoided by the use of barbiturates and vitamin C.

The authors conclude that 2 per cent intravenous Novocain is a useful antispasmodic drug which favors dilatation of the cervix in labor.

MAGIN SAGARRA

Pregnancy, Complications

Castledine, L. I. M., Hamilton-Paterson, J. L., and Rosser, E.: Acute Rheumatism in Pregnancy, J. Obst. & Gynaec. Brit. Emp. **58**: 253, 1951.

In ten years of obstetric practice in one hospital, 317 women with chronic rheumatic carditis have been under observation. In this series there were 7 deaths during pregnancy and 3 shortly after delivery. While there were no symptoms usually associated with active rheumatic fever, the pathological findings showed definite evidence of active rheumatism in all but one instance; 9 showed evidence of acute rheumatic carditis and in 6 this diagnosis was confirmed by histological findings (including typical Aschoff nodules); in the other 3 cases, fresh vegetations of the rheumatic type were found on the mitral valve and, in one of these cases, there was also a precardial effusion; in 5 of these cases there was also consolidation of the lung of the rheumatic type. In the one case without evidence of acute rheumatism, there was mitral stenosis with auricular fibrillation and death occurred early in pregnancy (eighth week) fourteen days after a hysterotomy. In the 307 women with chronic rheumatic carditis who survived and were followed up after delivery, there was no evidence of acute rheumatism in any case; all were given adequate antenatal care, and if evidence of decompensation developed they were kept at rest in bed until symptoms were relieved or until delivery (if symptoms occurred in the last two or three weeks of pregnancy). On the basis of these findings it is concluded that acute rheumatism resulting in acute lesions in the heart and/or lungs is the chief cause of death in pregnant women with chronic rheumatic carditis, rather than myocardial stress due to pregnancy in a patient with chronic valvular lesions.

HARVEY B. MATTHEWS

Hallum, J. L., and Newham, E. H.: Antenatal Thrombosis, J. Obst. & Gynaec. Brit. Emp. **58**: 278, 1951.

In the 13,144 deliveries at the Sorrento Maternity Hospital (Birmingham, England) in 1943 to 1950, there were only 5 cases of deep thrombophlebitis occurring during pregnancy; one of these was complicated by anemia. In another patient several pulmonary emboli occurred at the onset of labor with acute cardiac failure; the patient recovered, however, and four months later was free from symptoms. In 2 of these cases pain and swelling in the affected limb has persisted for several years after delivery. In one patient heparin was given during the puerperium with rapid improvement in the condition of the leg. The authors suggest the possibility of the antenatal use of heparin, if it does not result in placental or fetal hemorrhage.

HARVEY B. MATTHEWS

Wright, H. Payling: Venous Thrombosis During Pregnancy Treated With Dicoumarin, J. Obst. & Gynaec. Brit. Emp. **58**: 272, 1951.

A modified dicoumarin product, B. O. E. A. (Bio-3, 3′-[4-oxycoumarinyl] ethyl acetate) was used in the treatment of 9 cases of acute venous thrombosis occurring in various stages of pregnancy. With B. O. E. A., the average time for the maximal effect of a single dose was reduced to sixteen hours. Prothrombin estimations were made daily in all cases, and the dosage used was sufficient to keep the prothrombin level between 30 and 40 per cent of normal,

a somewhat higher level than usually employed in dicoumarin therapy, but considered to be safer for pregnant patients because of the danger of hemorrhage. The dosage employed to attain this level was 0.3 to 0.6 Gm. daily or every other day; the duration of the treatment was from five to eighteen days, the dosage being reduced gradually so that the prothrombin level returned to normal slowly. In all cases, the acute symptoms of pain and swelling subsided, and the patient was ambulatory before treatment was stopped. While in severe cases patients were kept in bed with a foot cradle for the first few days, all were being given massage and performing pedaling movements of the feet by the fifth day; and walking was permitted in a week in all cases. All these patients were delivered at term; there was one fetal death; all the other infants were normal. The cause of fetal death was a tentorial tear, but the extent of the hemorrhage may have been unfavorably affected by the infant's lowered prothrombin time. As this was the only case in which the anticoagulant was given just before term and was stopped only forty-eight hours before labor, and anticoagulant therapy in the earlier stages of pregnancy did not affect the infant unfavorably, the author is of the opinion that dicoumarin or allied substances should not be employed for a few days prior to the onset of labor. Earlier in pregnancy, the treatment was found not to be "unduly hazardous" if the prothrombin level is carefully controlled by daily determinations and treatment is not prolonged.

HARVEY B. MATTHEWS

Duek, H.: Two Cases of Ovarian Pregnancy at Term, Obst. y ginec. latino-am. **8:** 402, 1950.

The author, of Rio de Janeiro, reports two cases of ovarian pregnancy at or past term. Both cases were proved at operation and in each instance fulfilled Otto Spiegelberg's criteria of ovarian pregnancy (Arch. f. Gynäk., vol. 13, page 73). The first case concerned a Negro patient of 47 years of age who had carried the fetus for over 6 years. The fetus was mummified and intact. This patient died following laparotomy. In the second case, a white woman 11 months pregnant survived operation. This fetus was intact though dead. These two cases represent the fourth and fifth ovarian pregnancies reported in Brazilian literature and are the only ones in the literature wherein the fetus reached full-term age.

The article is especially valuable for it contains a summary of the references of the world literature on this rare topic. In his discussion of the history of ovarian pregnancy, Duek returns to the first case reported in 1614 by Mercerdus and a second case discussed by St. Maurice in 1682. Six photographs accompany the article.

CLAIR E. FOLSOME

Toxemia

Browne, O'Donel: Toxaemic Accidental Haemorrhage, Irish J. M. Sc. p. 113, March, 1952.

This is an important and forcefully written article indicating a change in thinking on the part of the Master of the Rotunda Hospital in regard to toxic accidental hemorrhage. For many years, in fact, since the teachings of Tweedy and FitzGibbon, the Rotunda Hospital has advocated the conservative approach to this complication. Rupture of the membranes and stimulation of labor with pituitary extract in order to accomplish vaginal delivery have been the rule. With this treatment there has been maternal mortality of 8 per cent, and fetal mortality of 75 per cent. Neither these mortalities nor the incidence of the disease has changed in the years, as indicated in Table I.

The author reports 100 cases of toxemic accidental hemorrhage occurring during the first four years of his Mastership. There were eight cesarean sections done with the loss of two mothers, or a mortality rate of 25 per cent. With the greatest candor, the author states, "My eight laparotomies performed in accidental haemorrhage were performed as desperate

measures, in fact, belatedly, yet only two women died.'' In a similar group of five severe cases treated by the so-called conservative method the author lost three women, or 60 per cent. Scantiness of transfusion therapy is also indicated by the author.

TABLE I. TOXAEMIC ACCIDENTAL HAEMORRHAGE

MASTERSHIP	TOTAL DELIVERIES	TOTAL NUMBER OF CASES	PERCENTAGE INCIDENCE AGAINST TOTAL PREGNANCIES	MATERNAL DEATHS	PERCENTAGE FOETAL LOSS EXCLUDING NEONATAL DEATHS
FitzGibbon	12,670	65	0.5	7- 6	70.6
Solomons	15,167	167	0.98	4-19	70.7
Davidson	20,550	176	0.8	7- 9	85.3
Falkiner	26,195	147	0.5	6- 1	78.2
Browne (4 years)	15,928	100	0.5	7- 0	77.5

In conclusion, he advocates more ample transfusion and more rapid emptying of the uterus by cesarean section.

LOUIS M. HELLMAN

Govan, A. D. T., Mukherjee, C. L., Hewitt, J., and Harper, W. F.: The Humoral Origin of Hypertension in Toxaemia of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **58**: 216, 1951.

Determinations of serum gonadotrophins, urea clearance, water excretion, and blood urea were made on 140 patients in the last trimester of pregnancy. Twenty of these patients were normal; the remaining 120 showed hypertension. In these 120 cases the reaction of the patient to tetraethyl ammonium bromide was also determined. In all these 120 cases, the urea clearance was normal, and the blood urea ''well within normal limits.'' Four of these patients had essential hypertension; in this group the serum gonadotrophins were low, the rate of water excretion was normal, and there was no reaction to tetraethyl ammonium bromide. The remaining patients showed evidence of hypertensive toxemia; they were divided into two groups on the basis of the tests made. The largest group (102 patients) showed a high concentration of gonadotrophins in the serum, the rate of water excretion was diminished, and there was no reaction to tetraethyl ammonium bromide. The other small group showed a low concentration of serum gonadotrophins, with a diminution in the rate of water excretion, and a reaction to tetraethyl ammonium bromide similar to that found in normal pregnant patients. These findings indicate that the majority of cases of hypertensive toxemia in pregnancy are of humoral origin, related to overactivity of the anterior pituitary.

HARRY B. MATTHEWS

Schneider, C. L.: Fibrin Embolism (Disseminated Intravascular Coagulation and the Aetiology of Eclampsia, J. Obst. & Gynaec. Brit. Emp. **58**: 538, 1951.

In 2,219 deliveries at the Herman Kiefer Hospital, Detroit, during eight months, there were ''many'' patients with toxemia, but only 6 who developed eclampsia. In 4 of these 6 patients, there was a retroplacental hemorrhage with a placental infarct subtending it—the result of a partial or self-limiting abruptio placentae. In 3 patients in whom adequate determinations were made, there was a tendency toward relative fibropenia after convulsions occurred. In 4 patients in whom specimens of blood were examined shortly after convulsions, there was evidence of intravascular hemolysis, which was transitory; this was followed by an increased icteric index, which also persisted for less than twenty-four hours. Progressive anemia was also noted. Although there were more cases of self-limiting retroplacental hematoma in nontoxemic patients, the relative incidence was higher in toxemic patients, and especially in severe toxemia. Since severe fibrinopenia may result from disseminated intra-

vascular coagulation in cases of severe or complete abruptio placentae, the partial fibrinopenia noted in eclampsia may also be due to intravascular coagulation. The other laboratory findings noted in the cases of eclampsia also suggest that eclampsia may be mediated by thromboplastin and "fibrin embolism." Photomicrographs of the hematoma and its relationship to the split layer of the decidua are shown.

HARVEY B. MATTHEWS

Campbell, A. U., and Burton, C.: The Relative Merits of the Basal Narcotics in the Treatment of Eclampsia, J. Obst. & Gynaec. Brit. Emp. **59**: 30, 1952.

In 36 cases of eclampsia treated with Avertin, there was no maternal death; the dosage of Avertin employed in eclampsia is midway between that used for obstetric twilight sleep and the adequate dosage for basal anesthesia. The average dose is 5 ml. Avertin in a 2½ per cent solution; if the eclamptic convulsions recur or if the patient is very restless, the full dosage can be repeated in three hours. Avertin does decrease the number of spontaneous deliveries, especially in primigravidas. All of the 9 multigravidas who had antepartum or intrapartum eclampsia, in the authors' series of 36 cases, had normal deliveries. The primigravidas with antepartum or intrapartum eclampsia were not allowed to deliver spontaneously unless the fetus was premature and therefore small. Of nineteen primigravidas with this type of eclampsia, only three had normal deliveries; three were assisted breech deliveries; eight low-forceps deliveries and one midforceps; and four were delivered by cesarian section. This series also included 8 cases of postpartum eclampsia in which Avertin was not given until after delivery. The fetal mortality rate was 28.95 per cent, but most of these deaths were due to other causes, not to the use of Avertin, chiefly to marked prematurity and dystocia. Intravenous Pentothal has also been found effective in the control of the eclamptic fits. As the evidence indicates that the anticonvulsant action of Pentothal and Avertin cannot be attributed to anesthesia alone, it is concluded that since these drugs lower blood pressure and cerebrospinal fluid pressure, these are synergistic factors in their anticonvulsant action in eclampsia. Paraldehyde has not been found to be as effective an anticonvulsant in eclampsia as other basal narcotics and this is attributed to the fact that this drug does not have the same effect in reducing blood pressure and cerebrospinal fluid pressure as Pentothal and Avertin.

HARVEY B. MATTHEWS

Cooke, Willard R.: Observation on Various Modes of Treatment of Eclampsia, South. M. J. **45**: 654, 1952.

The article is based on 501 cases of pre-eclampsia and 238 cases of eclampsia and from this study the author attempts to deduce the regime of therapy which offers the most favorable outcome for mother and baby. The essential problem is the prevention of convulsions in the pre-eclamptic patient and the immediate and sustained relief of the convulsive state in the eclamptic patient. Limitation of the convulsions is the major factor in decreasing mortality, since in the wake of the convulsions follow the failing heart with its pulmonary edema and the thromboembolic phenomena which lead to death.

Prior to 1930 most of the cases of eclampsia were treated with morphine or chloral hydrate or sodium bromide, or a combination of these. The use of parenteral magnesium sulfate, in the opinion of the author, reduces the incidence of the progression of pre-eclampsia to eclampsia. Intravenous magnesium sulfate, if used in adequate dosage and without other treatment except intravenous glucose and reasonable analgesic and anestheic agents during labor, is more effective in reducing the mortality of eclampsia than are other forms of treatment. It is felt that the toxemic patient has a high resistance to magnesium poisoning and tolerates the drug well. As a precaution the patient is tested before the administration of the magnesium ion and calcium gluconate is kept on hand as a ready antidote. It is suggested that magnesium sulfate may neutralize or possibly alter the chemical composition of that unknown toxin of eclampsia.

Pregnancy is always terminated in cases of developed convulsion but it is essential that such termination be delayed until the patient has been free of convulsions for at least forty-eight hours and she has recovered from cardiac exhaustion and the chemicophysical pathologic state which follows as a direct result of violent and sustained skeletal muscle contraction. As in pre-eclampsia, vaginal delivery is to be preferred to cesarean section where cephalopelvic dystocia does not exist.

WILLIAM BICKERS

Tubal Insufflation

Walker, A. H. C., and Stout, R. J.: The Effects of Anaesthesia Upon Fallopian Tubal Motility, J. Obst. & Gynaec. Brit. Emp. **59**: 1, 1952.

A group of 280 women was studied by uterotubal insufflation before and after anesthesia, while another group served as controls. In each of the anesthetized women, two uterotubal insufflation tracings were made before the anesthetic was given, and a third tracing was made while the patient was under the influence of the anesthetic. Three tracings were also made in the controls; some of these controls were given the same premedication as was used in the anesthetized patients. The effects of nine anesthetics and two alkaloids (morphia and atropine) were studied. With morphia the chief effect was increased contractility; with atropine there was no spasmolytic action, as tubal peristalsis was not affected. Light ether anesthesia caused a marked reduction in tubal tone, an increase in frequency of contractions, but did not significantly alter the magnitude of the tubal contractions. Chloroform caused a small reduction in tubal tone, no definite increase in amplitude; these findings with chloroform were contrary to what was expected. Trichlorethylene (Trilene) caused some reduction in tubal tone, more than chloroform, but peristalsis was not altered. The only effect of nitrous oxide was to increase the amplitude of muscular contractions. Light cyclopropane anesthesia and thiopentone had no effect on tubal motility.

d-Tubo-curarine had a stimulating effect in increasing the amplitude of peristalsis, but in some cases it produced a transient inhibition of tubal tone. High spinal analgesia increased the amplitude of peristalsis to a greater degree than any of the agents used; but low spinal analgesia had only a doubtful effect on amplitude. In relation to the effect of the menstrual cycle, it was found that the magnitude of contractions was decreased in the premenstrual phase. There was high incidence of spasticity in the initial uterotubal tracings in this group of patients. Ether, chloroform, and Trilene tended to abolish this spasticity. For the relief of uterotubal spasm, repeated insufflations at the same session should be done, combined with the use of anesthesia if necessary.

HARVEY B. MATTHEWS

Items

Submission of Manuscripts

Readers are reminded that manuscripts should be sent to Dr. Howard C. Taylor, Jr., 622 West 168th Street, New York 32, New York, or Dr. William J. Dieckmann, 5841 Maryland Avenue, Chicago 37, Illinois, the co-editors of the JOURNAL.

American Academy of Obstetrics and Gynecology

More than 1,100 Fellows and nonmembers attended the First Annual Clinical Session of the American Academy of Obstetrics and Gynecology in Chicago, Dec. 15 to 17, 1952.

Robert A. Kimbrough, Jr., Philadelphia, was installed as the third president of the Academy. Bayard Carter, Durham, N. C., was chosen president-elect to take office a year from now.

Other new officers elected include: C. Paul Hodgkinson, Detroit, secretary; Charles D. Kimball, Seattle, assistant secretary; Joe Vincent Meigs, Boston, second vice-president. Re-elected were Howard Stearns, Portland, Ore., first vice-president, and Herbert E. Schmitz, Chicago, treasurer.

Five district officers also were elected: District Chairmen, John B. Montgomery, Philadelphia, and John I. Brewer, Chicago. New district vice-chairmen are Duncan E. Reid, Boston; Frank R. Lock, Winston-Salem, N. C.; and Willis E. Brown, Little Rock, Ark.

The Academy's Second Clinical Session will be held in the Netherland Plaza Hotel, Cincinnati, Dec. 14 to 16, 1953. Chairman of the Program Committee is Andrew A. Marchetti, Washington, D. C. Local Arrangements Chairman is Arthur G. King, Cincinnati.

Texts of formal papers presented at the First Clinical Session will be printed in the Academy's new journal, *Obstetrics and Gynecology*, beginning with the first issue in January, 1953.

Published monthly, the journal will be edited by Ralph A. Reis, Chicago. It will contain some 120 pages of scientific material in each issue, as well as other items of interest to physicians practicing obstetrics and gynecology.

Nearly 6,000 subscriptions already have been received, including 2,600 Fellow and more than 3,000 nonmember subscriptions. An impressive number of subscriptions have been received from outside the United States.

The following educational scientific exhibits were given awards for excellence at the First Clinical Session:

First place: "Significance of Circulatory Phenomena in Abruptio Placentae," Charles L. Schneider, M.D., Ruby E. Engstrom, M.D., and Robert G. Braden, M.D., of Wayne University, Detroit, and Wayne County General Hospital, Eloise, Mich.

Second place: "Pregnancy in the Bicornuate Uterus," Frederick H. Falls, M.D., and Miss Charlotte S. Holt, of the University of Illinois College of Medicine and Illinois State Department of Public Health, Chicago.

Third place: "Pathology of Ovarian Tumors," Edward G. Winkler, M.D., and Gordon J. Hippert, M.D., of the University of Buffalo School of Medicine, Edward J. Meyer Memorial Hospital, and Sisters of Charity Hospital, Buffalo, N. Y.

Honorable Mention: "A Simple Test for Early Pregnancy, Ovulation, and Estrogen Activity by the Use of the Cervical Mucus Secretion," Maxwell Roland, M.D., of New York Post-Graduate Medical School, New York University-Bellevue Medical Center, and Queens General Hospital, New York, N. Y.